THE SYNTHESIS OF (±) - CLOVENE

THESIS

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for the degree of Ph.D.

by

Peter Doyle

1963.

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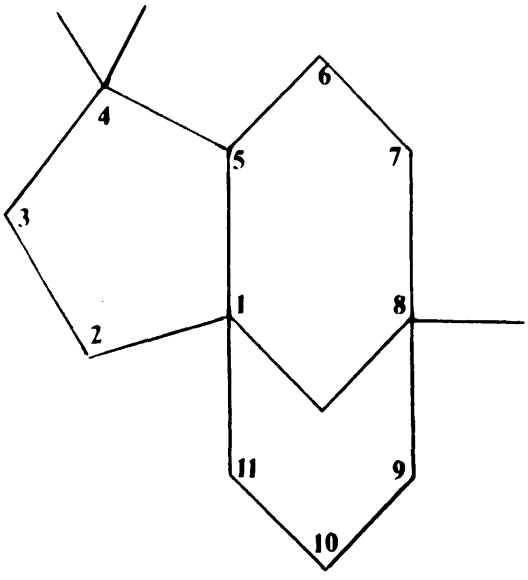

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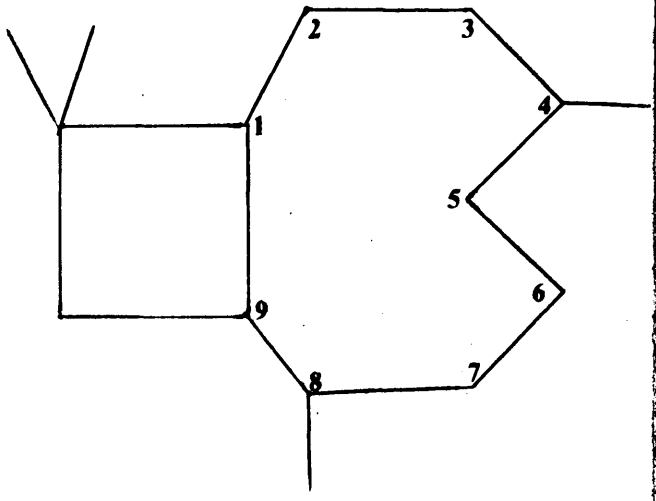

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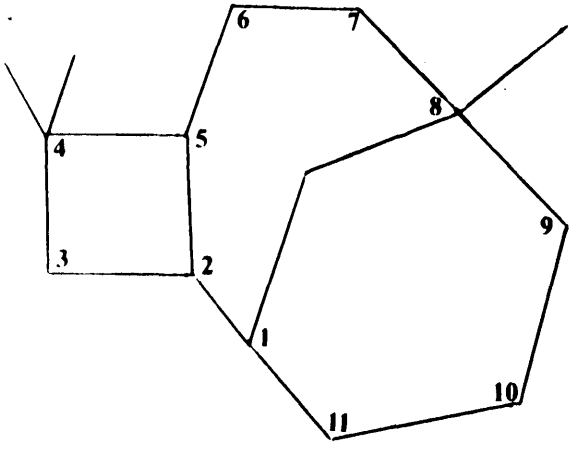

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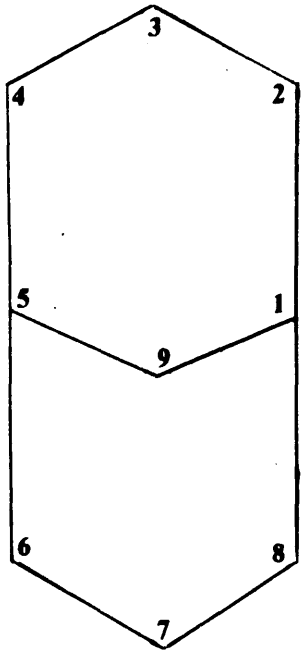


BICYCLO (3,3,1) NONANE

INTRODUCTION TO THE CHEMISTRY OF CLOVENE

"Clovene" is the trivial name, invariably used in place of the cumbersome systematic description, 4,4,8 - trimethyltricyclo $(6,3,1,0^{1,5})$ dodec-2-ene, for the olefinic rearrangement product (1) obtained together with caryolan-1-ol (2) by sulphuric acid treatment [1] of caryophyllene (3), the major constituent of oil of cloves. Although it was early characterised as a stable tricyclic compound, b.p. 261-263°, n_{25}^{D} 1.4913, $[\alpha]_D$ -23°, containing one cis disubstituted double bond,[2] it is evident that a structural elucidation of clovene (1) through controlled oxidative degradation would have been virtually impossible, because of the environment of the double bond, the only site amenable to attack. The structure of clovene was, in fact, postulated and confirmed in the course of a series of studies [3,4,5,6,19] by Barton and his collaborators, which established the total structure of caryophyllene (3). This latter structure has now been confirmed by the recent elegant synthesis by Corey and his co-workers.[7]

For over a century, prior to 1847, investigations on caryophyllene had been directed towards rationalising the numerous products obtained from the sesquiterpene by a variety of oxidation techniques.[2] In 1947, however, Treibs [8] found that the crystalline monoepoxide (4) of caryophyllene could be oxidised to formaldehyde and a crystalline keto-epoxide, $C_{14}H_{22}O_2$(5). This observation laid the foundation for the modern phase of the structural elucidation, in which investigators, principally Barton and his co-workers, directed their efforts towards rationalising the complex skeletal transformations undergone by caryophyllene and its derivatives.

Besides confirming the presence of an exo-methylene function, Treibs' work enabled Sorm to propose a tricyclo (7,2,0) undecane skeleton for caryophyllene, on the basis of the close similarity between the carbonyl regions of the infra-red spectra of (5) and cyclononanone.[9] In addition, the availability of this keto-epoxide enabled Barton to carry out a series of rearrangements[3,4] which initially confirmed and then extended Sorm's[9] proposal. Barton's successful interpretation of these skeletal rearrangements, coupled with controlled oxidative degradations,[4,6] led to the unequivocal establishment of structure (3) for caryophyllene, which is identical to that first proposed by Dawson, Ramage and Wilson,[10] but different from those suggested by Sorm.[9]

During the caryophyllene investigations, Barton suggested, on conformational grounds, that the formation of clovene (1) and caryolan-1-ol (2) arose from two modes of cyclisation, dependent on alternative conformations of the nine membered ring.[6] Similarly the two crystalline diols (6,7), obtained as by-products in the epoxidation of caryophyllene,[5,8] were seen to be produced by strictly analogous rearrangements during peracid treatment.

Since the plane of the endocyclic double bond is normal to the plane of the four-membered ring in the probable conformations (3a, 3b) of caryophyllene[6], the methyl group at C-4, depending on the conformation adopted, projects upwards or downwards with respect to the β- hydrogen atom on C-1. In a rearrangement of the latter conformation (3a), β- attack by an electrophile, OH^+ or H^+, on the endocyclic double bond induces α- attack on C-4 by the developing methylene bridge. Subsequent bond shift from C-9 to give β- attack on C-8, followed by hydration or proton loss, completes the formation of clovan-2 β, 9α-diol(6) or clovene, as the case may be.

Cyclisation in the other conformation (3b) produces a β- orientated methylene bridge which prohibits a bond shift to C-8, but permits nucleophilic attack to insert the hydroxyl groups of caryolan-1-ol (2) and caryolan-1,9β -diol (7).

The above scheme [6] is a development of earlier conceptions of the caryophyllene rearrangements,[4] in which clovene and caryolan-1-ol were believed to result from the same intermediate carbonium ion (3c). A careful repetition of the dehydration of caryolan-1-ol, however, enabled Lutz and Reid to show that contrary to reports in the earlier literature, clovene was not a dehydration product of caryolan-1-ol, and that the caryolane skeleton could not be rearranged to that of clovane.

On the basis of this evidence, Barton proposed the two independent cyclisation mechanisms described above.[6] The conclusion that the resultant caryolane and clovane skeletons possessed methylene bridges of opposite configuration, was fully upheld by subsequent molecular rotation studies.[14]

Structural correlation between caryolan-1-ol (2) and caryolan-1,9β-diol (7) was obtained as follows. Oxidation of the diol furnished a ketol (8) which gave caryolan-1-ol on Wolff-Kishner reduction and a non-enolisable but epimerisable keto-acid, $C_{13}H_{20}O_3$ (9) by further oxidation with selenium dioxide and permanganate.[4] X-ray investigation[15] of 1-chlorocaryolane and 1-bromocaryolane provided the final corroboration of these structures, and simultaneously confirmed the stereochemistry of the ring junction in caryophyllene, since C-2 and C-5 are not involved in the caryolane cyclisation.[6]

The structural relationship between clovene and clovan-2β, 9α-diol (6) was established by the following transformations.[5] Oxidation of the diol furnished a diketone (10) which on Wolff-Kishner reduction afforded clovane (11) identical with the product of hydrogenation of clovene.[11] Selective oxidation of the diol (6) yielded a ketol (12, R=H), $\nu_{max.}$ = 1730 cm^{-1} (cyclopentanone); acetylation of the ketol, and exhaustive bromination furnished a dibromoketone (15) confirming the presence of two hydrogen atoms adjacent to the carbonyl function. Similarly, bromination of the crystalline diketone (10), $\nu_{max.}$ = 1730, 1702 cm^{-1} (cyclohexanone), yielded a crystalline tetrabromide, illustrating the presence of two hydrogen atoms adjacent to the cyclohexanone carbonyl grouping.[5] The acetoxyketol (12, R=CH_3CO) was oxidised with selenium dioxide and the resultant α-diketone (13) cleaved with alkaline peroxide; hydrolysis, oxidation, and Wolff-Kishner reduction completed a sequence[6] which provided a product identical with clovenic acid (14), obtainable by direct oxidation of clovene (see below).[16]

Both the structure and the stereochemistry of clovan-2β,9α-diol (6) were confirmed by a controlled degradation[6] of the derived diketone (10). Oxidative cleavage of this latter compound yielded a keto-dicarboxylic acid (16) which on successive treatments with selenium dioxide and alkaline peroxide furnished a tetracarboxylic acid (17). Pyrolysis at 270° produced a smooth cyclisation to a keto-dicarboxylic acid (18) which did not form an anhydride on fusion. Oxidation of the cyclopentanone ring was accomplished as before by selenium dioxide and alkaline peroxide.

Decarboxylation, with concomitant aromatisation, of the tetra-carboxylic acid (19) furnished p-cymene, which was identified by infra-red and ultra-violet spectroscopy, and by oxidation to terephthalic acid.

The limited information provided by clovene itself was derived from clovenic acid (14), its product of oxidation.[16] The resistance of this acid to further oxidation[23] or bromination,[16] and the formation of a very stable anhydride rather than a ketone on pyrolysis,[16] suggested a ditertiary acid formed by cleavage of a cyclo pentene ring. In an attempt to corroborate Barton's work, Lutz and Reid[11] undertook a degradation sequence starting from clovenic acid (14). Lithium aluminium hydride reduction furnished a diol (2) which was expected to undergo dehydration-rearrangement to a mixture of olefinic alcohols. It was hoped that one of these (21) could then be oxidised to a keto-acid containing a cyclo-hexanone ring (22). This objective was not, however, achieved, since dehydration of the diol (2) yielded a cyclic ether which on oxidation furnished an inert lactone (23) and a degraded acid, $C_{13}H_{20}O_5$.

Since much of the early work on caryophyllene and clovene was carried out before the advent of infra-red spectroscopy and gas-liquid chromatography, it is inevitable that reliance on boiling points, refractive indices, and optical rotations as a means of identification, should have resulted in a number of discrepancies in this field.

In the early work Deussen showed that caryophyllene from oil of cloves consisted of three main components;[17] a high-boiling optically inactive component, α-caryophyllene, which he identified with a hydrocarbon isolated from oil of hops, humulene, and two lower-boiling optically active components, β- and γ- caryophyllene, later renamed caryophyllene and isocaryophyllene respectively.[5] That the impure nature of normal caryophyllene did not invalidate the results of oxidative degradation was shown by Ramage and Simonsen,[18] who obtained the same C_{14} and C_{11} acids by ozonolysis of a pure crystalline carophyllene nitrosite, as were obtained by degradation of the caryophyllene mixture. Lutz and Reid[11] were likewise able to show that the clovene normally obtained by acid rearrangement of caryophyllene was a complex mixture of hydrocarbons. For the purpose of comparison, they prepared the first crystalline derivatives of clovene, the diastereoisomeric dibromides of melting points 41 - 43° and 70 - 72°, which on zinc dust treatment regenerated clovene, identical in infra-red spectrum, and similar in refractive index to a sample prepared by Eschenmoser[19] by careful but tedious fractionation. The carefully purified clovene was found to give a high yield of clovenic

acid on oxidation; the varying low yields of acid reported in the literature reflect the variable proportion of isomeric impurities in the samples of "clovene" employed.

Besides providing a method of identifying and purifying clovene, Lutz and Reid demonstrated conclusively that, contrary to reports in the literature,[12,13] dehydration of caryolan-1-ol did not give isoclovene and clovene, but isoclovene and an isomeric compound which they termed pseudoclovene.[11] The latter compound, although similar in physical properties to clovene, reacted with N-bromosuccinimide, and on oxidation afforded an oily dicarboxylic acid which could be brominated by the Hell-Volhard-Zelinski technique. With this evidence available, Lutz and Reid proposed the structure,(24) for pseudoclovene, the simplest constitution consistent with the known facts.

The structure of the unstable isoclovene (25) was established by X-ray studies[20] of the crystalline hydrochloride and hydrobromide[12]. The suggested skeletal transformation which gives rise to isoclovene exemplifies some rather unusual features of carbonium ion rearrangements.[20]

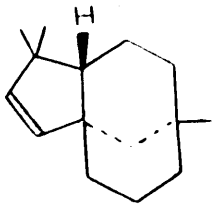
Although the structures of caryophyllene and its rearrangement products were unequivocally established despite the presence of impurities in the caryophyllene, a sufficient number of discrepancies have arisen to cause confusion regarding both the structure and the origin of the so-called α-caryophyllene alcohol, which has been reported by numerous workers[1,4,21,11] as an acid rearrangement product of caryophyllene.

In the course of the work on caryophyllene Barton suggested that α-caryophyllene alcohol had the constitution clovan-2-ol(26), a formulation in accordance with the reported facts. Thus α-caryophyllene alcohol, $C_{15}H_{26}O$, was a saturated, tricyclic, secondary alcohol, which on dehydration was stated to give clovene, and on vigorous oxidation, clovenic acid.[21] Two years later, however, Barton and Nickon[14] prepared the epimeric clovan-2-ols, m.p. 96-97° and 97-98°, and showed that neither was identical with α-caryophyllene alcohol, m.p. 117°. In the light of these facts, the work of Dev,[22] who in 1951 obtained a compound, apparently identical with α-caryophyllene alcohol, by acid rearrangement of humulene(27), assumed a new significance, since humulene is normally present as an impurity (up to 5%) in caryophyllene.

Work in these laboratories has been directed toward establishing the origin of α-caryophyllene alcohol. Samples of caryophyllene and humulene were purified and their homogeneity confirmed by gas-liquid chromatography. Treatment of pure samples of each with sulphuric acid under identical conditions[1] showed that humulene alone furnished crystalline, optically inactive, α-caryophyllene alcohol. Such a result plainly demanded repetition of the dehydration of the alcohol under the conditions reported in the literature.[12] Analysis of the dehydration product by gas-liquid chromatography revealed a mixture of four components, none of which exhibited the same retention time as authentic clovene.

For this reason, it is difficult to rationalise the results of Bell and Henderson[21] who oxidised α-caryophyllene alcohol to clovenic acid and clovenic anhydride m.p. 50-51°, identical in melting point and mixed melting point with authentic samples prepared by Ruzicka.[16] Such a result is plainly incompatible with the synthetic work hereafter described, since the synthetic (±) - clovenic anhydride obtained exhibited a melting point of 76-78°. Clearly, since α-caryophyllene alcohol is the product of rearrangement of an optically inactive compound, humulene, it must be a racemate, and if, therefore, it did furnish clovenic anhydride on oxidation, the melting point should correspond to that of the racemic synthetic compound, m.p. 76-78°, rather than to that of the optically active anhydride, m.p. 50-51°.

Currently, X-ray investigation of a heavy atom derivative of α-caryophyllene alcohol is being undertaken, to establish the structure of this controversial compound.



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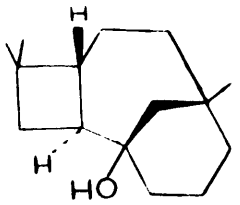

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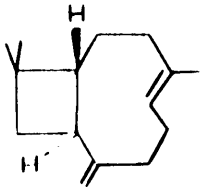

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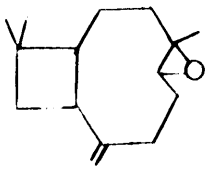

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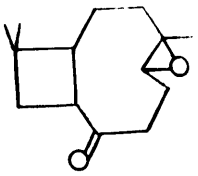

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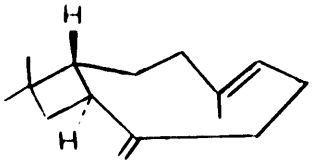

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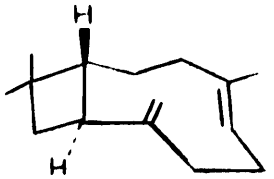

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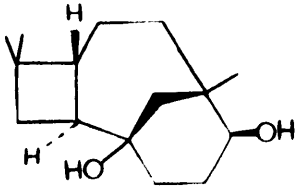

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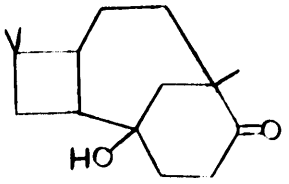

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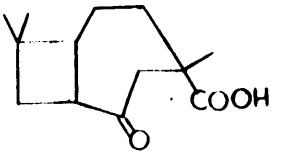

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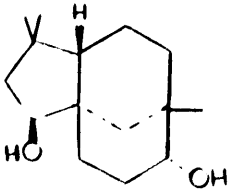

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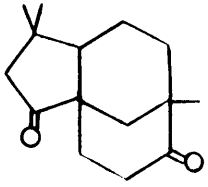

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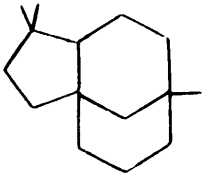

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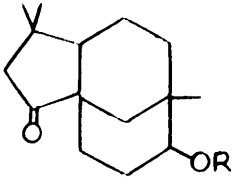

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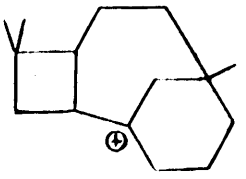

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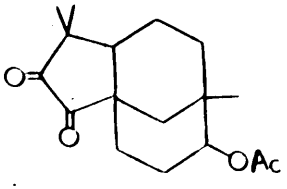

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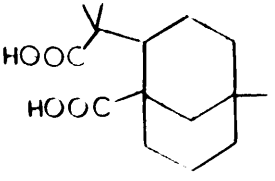

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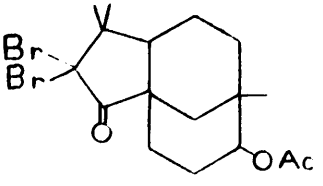

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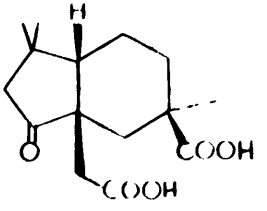

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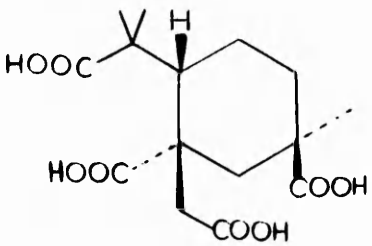

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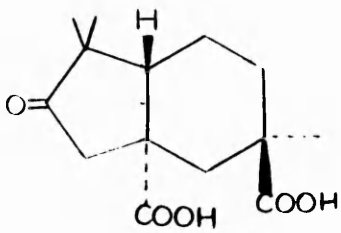

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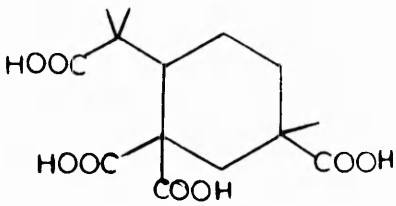

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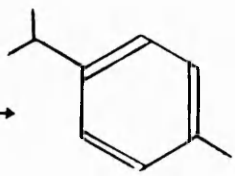

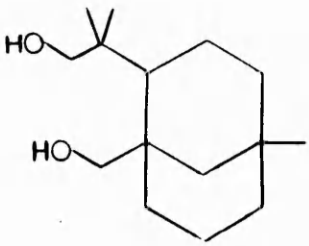

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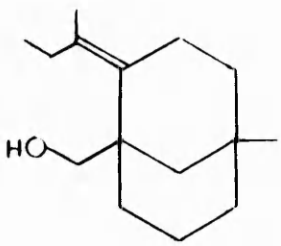

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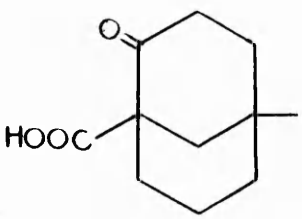

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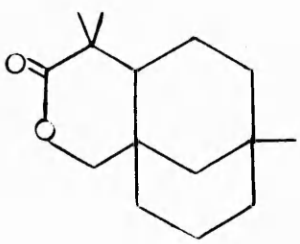

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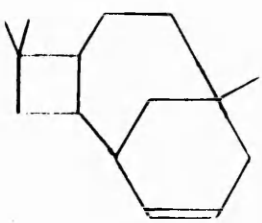

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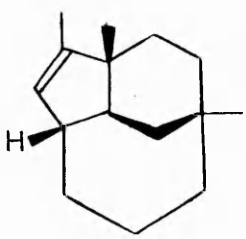

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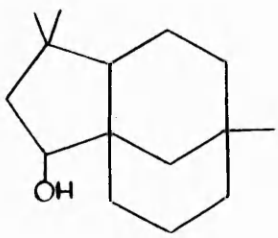

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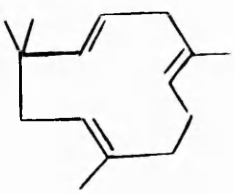


27

THEORETICAL.

Current interest in this department in bridged ring compounds and the unique tricyclic ring system of clovene (1) combined to stimulate interest in the synthesis of this sesquiterpenoid artefact. A logical appraisal of this problem demands the pursuit of one or other of two synthetic schemes: the clovene skeleton may be constructed by elaboration of a suitable bicyclo (4,3,0) nonanone, containing the geminal dimethyl grouping, but requiring stereospecific annellation to attach the third ring. Alternatively, the use of a bicyclo(3,3,1)nonane precursor limits the stereochemical problems but necessitates unequivocal introduction of the geminal dimethyl grouping at a later stage.

The initial synthetic incursions[24] into this problem followed the latter scheme, in which 5-methyl-3-ketobicyclo-(3,3,1)nonane-1-carboxylic acid (2,R=OH) was chosen as a suitable starting material. Methyl 3-methylcyclohexan-1-one-3-acetate (3) was condensed with malononitrile to give the unsaturated dinitrile (4) which reacted with sodium cyanide in dimethylformamide to yield a crystalline but inseparable mixture of isomeric trinitriles (5). Vigorous acid hydrolysis, followed by esterification, and Dieckmann cyclisation afforded the expected mixture of bicyclo keto-esters. Further hydrolysis and simultaneous decarboxylation yielded a mixture of products from which the desired keto-acid (2,R=OH) was obtained by crystallisation.

Extension of the side chain for construction of the requisite

diketone (7), which was expected to cyclise by an intramolecular Michael reaction, was accomplished by addition of isobutene to the keto-acid chloride (2,R=Cl). Purification and dehydrochlorination of the resultant chlorodiketone (8) were effected by chromatography on alumina which offered the simplest route from (8) to the diketone (7). It was found, however, that the steric interaction between the 2-methylene grouping and the terminal isopropylidene function prevented cyclisation of (7) under either acidic or basic conditions. To overcome the steric problem, and simultaneously encourage irreversible cyclisation by an S_N2' reaction, the ketone (7) was converted in two steps to the more flexible brosylate (9,R=p-$BrC_6H_4SO_2$) and tosylate esters (9,R=p-$CH_3C_6H_4SO_2$). Despite the presence of a good 'leaving' group, however, base catalysis failed to induce the necessary cyclisation by the anion of (9) in either case. In fact the product obtained from both esters was shown[25] to be the conjugated diene (10).

Although this 3-ketobicyclo(3,3,1)nonane approach had not afforded a tricyclic product the keto-ester (6,R=CH_3) provided invaluable information about 2-ketobicyclo compounds. Treatment of the derived keto-acid chloride with aluminium chloride gave the chlorolactone (11), demonstrating the feasibility of the desired type of ring formation when the necessary activation was available. Thus if extrapolation from a bicyclo(3,2,1)octane system to a bicyclo(3,3,1)nonane one were permissible, the diketone (12,R=H) ought to undergo facile cyclisation to give a tricyclic compound

(24,R=CH_3) suitable for further elaboration.

Accordingly, 2-carbethoxy-6-methylcyclohexanone was prepared by glyoxylation of 2-methylcyclohexanone and thermal decarbonylation of the intermediate α-keto-ester. The doubly activated 2-methine grouping of the β-keto-ester permitted a Michael addition to acrolein to proceed at low temperature; the resulting aldehyde (13) was then cyclised by means of cold concentrated sulphuric acid to afford a mixture of the required bicyclo(3,3,1)nonane keto-ester (14,R=C_2H_5) an isomeric bicyclo(3,2,1) compound (15), and an aromatic acid (16)[26]. Since the carbonyl function of the bicyclo-(3,3,1)nonane keto-ester (14,R=C_2H_5) is subject to considerable steric hindrance, separation of the keto-esters was readily achieved through selective semicarbazone formation by the α,β-unsaturated ketone (15). Thus, despite the inconvenience introduced by these rearrangement products, satisfactory amounts (300 g.) of the 9-keto-ester (14,R=C_2H_5) could be obtained by this drastic cyclisation procedure.

Although β-keto-esters are generally unstable to both acid and base, it was confidently expected that hydrolysis of the ester (14,R=C_2H_5) would proceed without disruption of the bicyclo nucleus, since Cope and Synerholm[27] had shown that the analogous 5-desmethyl ester underwent hydrolysis without ring-fission. The bicyclo keto-acid (14,R=H) was in fact obtained as a crystalline solid m.p. 139-143°, and no cleavage products were isolated. Such stability is a consequence of the steric factors summarised in Bredt's rule[28] and is observed in other β-keto-acids possessing a bridgehead carboxyl

group.[29]

At this stage in the sequence, the 9-keto function, essential for construction of the bicyclo system, but now no longer desired, was removed by Clemmenson reduction of the acid; the possible alternative, Wolff-Kishner method involving the action of hydrazine on the keto-ester (14,R=C_2H_5) failed, the only product being the pyrazolone (17). The product of Clemmensen reduction consisted mainly of three acids, the 9-methylene (19,R=H), 9-keto and 9-hydroxyl (18,R=H) compounds; to facilitate separation, the mixture was esterified and the resulting mixture of esters reduced with sodium borohydride. Separation of the two-component mixture was accomplished by chromatography on alumina; only the 9-methylene ester (19,R=CH_3) was eluted by light petroleum and its purity was established by gas-liquid chromatography.[24]

Since an effective method of preparation of a bicyclo(3,3,1)non-3-ene intermediate had been devised, completion of the projected synthesis now hinged on the introduction of an oxygen function in the 2-position of the olefin ester (19,R=CH_3). After several unsuccessful efforts to effect direct allylic oxidation to the α,β-unsaturated keto-ester (20,R=CH_3) by means of t-butyl chromate[31] and chromium trioxide in acetic acid,[32] a stepwise procedure was developed in which the keto-ester (20,R=CH_3) could be obtained in acceptable yield. Treatment of the olefin ester with t-butyl perbenzoate in the presence of cuprous bromide,[33,35] and methanolysis[50] of the resulting viscous diester (21,R=CH_3, R'=C_6H_5CO) gave the allylic hydroxy-ester (21,R=CH_3, R'=H) which was quantitatively

oxidised to the desired α,β-unsaturated keto-ester (20,R=CH_3) by manganese dioxide,[34] the product exhibiting ultra-violet absorption at 230 mμ (7,370). Confirmation that the oxidation had furnished the 2-keto-ester, was obtained by catalytic hydrogenation to a β-keto-ester (22,R=CH_3) which reacted readily with hydrazine to form a crystalline pyrazolone (23).

Unfortunately, attempts to exploit the 2-keto function by a Reformatski reaction with ethyl α-bromoisobutyrate proved uniformly unsuccessful; despite an apparently vigorous reaction, no useful product was isolable, and this approach was therefore summarily abandoned. Likewise, projected alkylations of the enamine of acetone by the mesylate or tosylate of the allylic alcohol (21,R=CH_3, R'=H) were frustrated at the outset by the failure of the alcohol to react with the appropriate sulphonyl chloride.

The complete lack of success enjoyed in this approach prompted the adoption of a second method of elaboration[36] in which the objective was the dione (12,R=H) (a 4-5-seco clovane), capable of undergoing intramolecular aldol condensation to the tricyclic 4-desmethylclov-4-en-3-one (24,R=CH_3). Although the isopropyl ketone (12,R=CH_3) would in principle have been the ideal precursor for a clovene skeleton, use of such a compound would inevitably have prohibited formation of an α,β-unsaturated ketone, and might have precipitated the sort of steric complications previously encountered.[24] In the case of the ethyl ketone (12,R=H), the clovane skeleton would be readily obtainable from the 4-desmethyl compound (24,R=CH_3) by

methylation, since alkylation of a system of this nature is known to produce the geminal dimethyl ketone, rather than the α,α'-dimethyl compound.[37]

As a first step towards the necessary diketone (12,R=H), the olefin acid (19,R=H) was homologated by an Arndt-Eistert sequence: treatment of the acid with oxalyl chloride gave quantitative conversion to the acid chloride which provided a yellow crystalline diazoketone by the action of diazomethane. The Wolff rearrangement to the homologous olefin ester (25,R=CH_3, R'=H) was accomplished by addition of a saturated solution of silver benzoate in triethylamine[38] to a solution of the diazoketone in anhydrous methanol. The ester was obtained free of a lactonic impurity (infra-red absorption at 1770 $cm.^{-1}$), by chromatography on alumina, from which only the ester was eluted by light petroleum. Chain extension was completed by acylation of cadmium diethyl[37,40] by the derived acid chloride to give an excellent yield (80%) of the monoketone (26,R=H).

In view of its successful application to the olefin ester (19,R=CH_3) t-butyl perbenzoate was the obvious reagent for attempted allylic oxidation of the ketone (26,R=H). The resulting keto-benzoate (26,R=C_6H_5COO) was obtained as a partly solid epimeric mixture which, by successive treatments with sodium borohydride and aqueous base, furnished a partially crystalline diol (27). Oxidation, followed by catalytic hydrogenation of the resulting enedione (63,R=C_2H_5) $\lambda_{max.}$ 228-232mμ(2,500) completed the preparation of the diketone (12,R=H). Analysis by gas-liquid

chromatography, however, confirmed the suspicion engendered by the low intensity absorption of the enedione (63,R=C_2H_5) namely, that the final product was far from homogeneous.

After several fruitless attempts to purify the dione (12,R=H) the crude material was employed for base-catalysed ring closure; this gave a product exhibiting ultra-violet absorption in the expected region, 241-245mμ. Careful chromatography ultimately provided a small quantity of the cyclopentenone (24,R=CH_3) which was characterised through its dark-red, 2,4-dinitrophenylhydrazone, m.p. 223-225°.

As had been anticipated, base catalysed methylation of the α,β-unsaturated ketone (24,R=CH_3) gave exclusively the geminal dimethylcyclopentanone (28) which displayed carbonyl absorption in the infra-red at 1740 $cm.^{-1}$, and gave a yellow crystalline 2,4-dinitrophenylhydrazone. A paucity of material, however, and the doubtful purity of that which was available, prevented further progress towards clovene, the synthetic goal.

In spite of these obstacles, the results of this approach[36] had justified the use of a 2-ketobicyclo intermediate and had, furthermore, demonstrated the feasibility of ring formation through the diketone (12,R=H). If a successful route to this precursor could be devised, every indication suggested the possibility of successful completion of the synthesis.

Although the results obtained through the use of a bicyclo (3,3,1)nonan-2-one precursor augured well for subsequent extension and improvements it was, nevertheless, deemed expedient to investigate the alternative approach to clovene by way of a bicyclo(4,3,0)nonane precursor, while further studies on the former system were conducted. Since the substituted indanone (29) seemed eminently suitable as a starting material, efforts were directed towards the preparation of β-(3-methoxy-4-methylphenyl)-isovaleric acid (30,R=CH_3O;R'=OH) which could be expected to cyclise to the indanone (29). A Friedel-Crafts reaction between toluene and mesityl oxide[41] readily afforded 4-methyl-4-(p-tolyl)-pentan-2-one (30,R=H,R'=CH_3) which on treatment with sodium hypobromite[42] furnished crystalline 3-methyl-3-(p-tolyl)isovaleric acid (30,R=H,R'=OH). The latter, however, failed to give a homogeneous product on nitration and thus precluded the standard sequence: nitro compound-amine-phenol-methyl ether. The desired acid (30,R=CH_3O, R'=OH) was, in fact, obtained by an alternative route starting from 3-amino-4-methylacetophenone,[43] which was converted in two steps to 3-methoxy-4-methylacetophenone.[44] This compound condensed with both ethyl cyanoacetate and malononitrile to give low yields of the expected products (31,R=$COOC_2H_5$; R=CN). The latter reacted with excess methylmagnesium iodide to give a good yield of the saturated geminal dimethyl compound (32, R=CN) by conjugate addition to the bond. Prolonged vigorous hydrolysis furnished the expected dicarboxylic acid which decomposed at 160° to carbon dioxide and β-(3-methoxy-4-methylphenyl)isovaleric acid (30, R=CH_3O, R'=OH). Because of the

poor yields in this series, and the encouraging results in concurrent work, this approach was pursued no further, although the required starting material had been attained.

In this context the work of Dutta and his colleagues[45] is worthy of mention. In a similar scheme β-(p-anisyl)isovaleric acid (33) obtained via conjugate addition of methylmagnesium iodide to the cyano-ester (34), was cyclised by polyphosphoric acid to the indanone (35), which gave the α,β-unsaturated ketone (36) by hydrogenolysis and Birch reduction. Further elaboration was accomplished by simultaneous conjugate cyanide addition to the double bond and conversion of the ketone to the cyanohydrin by means of sodium cyanide in aqueous ethanol. Hydrolysis, esterification and two-stage reduction gave a diester (37, R'=R'' $=CH_3$, R=H) which was selectively hydrolysed to the acid-ester (37, R=H, R'=H, R'' = CH_3). Introduction of the potential bridgehead methyl group of clovene was accomplished by a Favorski rearrangement of the Chloromethyl ketone (38), obtained in three steps from the acid-ester. The yield of the derived ditertiary ester (37, R=R'=R' = CH_3) was, however, unexpectedly poor, the product consisting mainly of the alternative primary ester (39).

The cis relationship of the ester groupings in the former was demonstrated by the facile anhydride formation (40) of the derived acid, but no evidence was presented to confirm that cyanide addition resulted in a cis-fused bicyclo(4,3,0)nonane skeleton. Thus since conjugate cyanide addition to the octalone (41) and cholest-4-en-3-one (42) has been shown[46,47] to furnish a mixture of cis and trans

isomers, the stereochemistry of the ring fusion in the diester (37, R=R' $=CH_3$) would seem at least debatable if not incorrect. Furthermore, although chain extension of the diester and ring formation by standard methods could be expected to furnish tricyclic material the lack of a suitable substituent in the cyclopentane ring would limit this route to the synthesis of the saturated clovane (43).

While the bicyclo(4,3,0)nonane approach was being pursued, efforts were directed towards satisfying what had emerged as the outstanding need in the bicyclo(3,3,1)nonane scheme - viz. the unequivocal introduction of an oxygen function in the 2-position. Since previous experience[36] had revealed the facility with which the diketone (12,R=H) gave tricyclic material, it was felt that an ideal intermediate would be the keto-acid (45, R=H), which predictably would be a crystalline, readily purified, solid.

In the course of the preparation of the olefin ester (19, R=CH_3), the possibility had been considered of reducing the 9-keto-acid (14, R=H) by the Wolff-Kishner method instead of by the laborious Clemmensen technique. It was found, however, that despite the use of anhydrous hydrazine,[48] the formation of a pyrazolone (17) still prevented reduction, as in the case of 9-keto-ester (14, R=C_2H_5). Since the homologous 9-keto-ester (44, R=CH_3) could not give such a stable derivative[49] the 9-keto-acid (14, R=H) was subjected to an Arndt-Eistert homologation, but the product was complex, consisting apparently of a crystalline lactone and the unhomologated 9-keto-ester. For this reason it

seemed wiser to carry out allylic oxidation on the homologated ester (25, R=CH_3, R'=H) itself rather than to attempt the homologation of the β-keto-ester (22, R=CH_3) made available by treatment of the olefin ester (19, R=CH_3) with t-butyl perbenzoate.

The encouraging results obtained[36] through the use of the latter reagent prompted a study of its behaviour towards the ester (25, R=CH_3, R'=H). Under conditions identical to those previously employed, the ester gave a product which furnished, after chromatography on alumina, the benzoyloxy-ester (25, R=CH_3, R'=C_6H_5COO) as a partially solid product, readily purified by crystallisation. Hydrolysis of the pure compound, m.p. 91-92°, gave a neutral fraction consisting of the crystalline lactone (46, R=H) of 2β-hydroxy-5-methylbicyclo(3,3,1)non-3-ene-1-acetic acid. Methanolysis[50] of the crude benzoate, however, gave a mixture of methyl benzoate, the lactone, and the 2α-hydroxy-ester (25, R=CH_3, R'=OH), readily separable by chromatography. Alternatively, direct alkaline hydrolysis of the oily mixture of epimeric benzoates afforded the lactone (46, R=H), benzoic acid and the crystalline 2α-hydroxy-5-methylbicyclo(3,3,1)non-3-ene-1-acetic acid. This latter structure (25, R=H, R'=OH) tentatively assigned to the acid on the basis of the known behaviour of t-butyl perbenzoate,[33,35] was confirmed at a later stage in the work.

Although this method had furnished workable quantities of the lactone, the moderate yields stimulated further investigation into alternative means of allylic oxidation which might provide the 2-keto-ester (48, R=CH_3) directly in good yield.

In the course of stereochemical studies on the α-amyrins Corey[52] had achieved excellent yields in the conversion of methyl acetyloleanate (47) to methyl acetyl-11-ketoöleanate by oxidation with sodium dichromate dihydrate in acetic acid. Application of this method to the homologated ester gave a good recovery (60%) of a neutral product, $\lambda_{max.}$ = 230-232 mμ (3,500). Chromatographic separation of the product furnished starting material and a mixture of the unsaturated keto-ester, (48, R=CH_3) $\nu_{max.}$=1725, 1670 cm.$^{-1}$ and a lactone, $\nu_{max.}$ = 1770 cm.$^{-1}$

On hydrogenation, the mixture rapidly absorbed an amount of hydrogen equivalent to 65% of the theoretical uptake, and hydrolysis of the product furnished a neutral fraction identical in melting point and infra-red spectrum to the lactone (46, R=H) previously obtained, and a liquid keto-acid which could not be induced to crystallise.

Since this keto-acid could not be satisfactorily characterised through spectroscopic or analytical data, attempts were made to confirm the position of the carbonyl function by the preparation of tricyclic derivatives. However, treatment of the acid with acetic anhydride containing fused sodium acetate[53] failed to yield any crystalline enol-lactone (49). Likewise the derived acid chloride, on treatment with aluminium chloride, furnished no crystalline chlorolactone analogous to that (11) obtained from the corresponding 2-keto bicyclo(3,2,1)octane acid.[25]

Despite the lack of crystalline products, it was felt that spectroscopic evidence of allylic oxidation justified further study

of methods of direct oxidation. After a fruitless attempt employing potassium chromate in refluxing acetic acid, encouraging results emerged from the reaction of the ester (25,R=CH_3, R'=H) with anhydrous potassium chromate in a mixture of acetic acid, acetic anhydride, and benzene.[54] Thus the ester, after treatment with this mixture for two days at 40°, gave an excellent recovery of a neutral product, $\nu_{max.}$=1725, 1670 $cm.^{-1}$, $\lambda_{max.}$=230-232 mμ(5,100), separable by alumina chromatography into a number of fractions with extinction coefficients ranging from 2,000 to 6,900. The purest fraction (ε 6,900) gave, on distillation, a colourless oil (ε 8,200) which underwent hydrolysis to a crystalline keto-acid, m.p. 160-161° (48,R=H). The latter furnished, by borohydride reduction in aqueous sodium bicarbonate solution, a hydroxy-acid (25,R=H, R'=OH) m.p. 142-144°, identical to that obtained directly from the *t*-butyl perbenzoate oxidation, and indirectly from the potassium chromate-acetic acid oxidation. Catalytic hydrogenation of the keto-acid (48,R=H) m.p. 160-161°, readily afforded the corresponding saturated keto-acid (45,R=H) m.p. 138-139° whose structure was later unequivocally established by its conversion to a crystalline enol-lactone (49), m.p. 32-34°.

Although seeding of various oily samples of the keto-acid (45,R=H) previously obtained, afforded further small quantities of crystalline material, the amount available was patently inadequate for long term work. At this juncture, therefore, it was inescapable that a successful completion of the synthesis demanded a method of allylic oxidation far more efficient than those so far employed.

Of the well-tried allylic oxidising agents, selenium dioxide had never been investigated in this context. Towards organic compounds, selenium dioxide exhibits a variety of behaviour, unequalled by any other reagent.[55,56] Besides being capable of carrying out direct oxidation, as for example the conversion of diphenylacetylene to benzil, or anthracene to anthraquinone, selenium dioxide can also effect dehydrogenation of cyclohexane derivatives to aromatics, and oxidation of 1,4-diketones, such as acetonylacetone, to the corresponding conjugated enediones.

Of particular relevance to the synthesis of clovene, however, were the oxidations of active methylene groups adjacent to carbonyl functions, aromatic rings and isolated double bonds achieved by this reagent. From a study of the allylic oxidation of olefins by selenium dioxide in acetic acid, Guillemonat[57] derived two empirical rules: firstly, that oxidation took place at the carbon atom adjacent to the more substituted carbon of the ethylenic linkage, and secondly that the oxidation of a terminal double bond afforded a mixture of products through double bond migration. These proposals were substantiated by the work of Colonge and Reymermier[58] who obtained only 2-methyl-pent-2-en-1, 5-diol (50,R=OH) from 2-methyl-pent-2-en-5-ol (50,R=H) but isolated both hex-2-en-1, 6-diol (52) and hex-1-en-3, 6-diol (51,R=OH), from the oxidation of hex-1-en-6-ol (51,R=H).

Fieser and his colleagues, having noted the highly specific oxidation of certain steroids possessing a 14α-hydrogen atom, investigated the facile oxidations in acetic acid of cholest-7-enol

(53) and methyl cholenate (54). In both cases[59,60] it was shown that the products were those of allylic rearrangement, which, these workers suggested, was preceded by a straightforward allylic oxidation, although in neither case could the possibility of double bond migration prior to oxidation be rigorously excluded. With the object of establishing a definite mechanism for such oxidations, Nelson and Trachtenburg[61] examined the behaviour of optically active carvomenthene (55,R=H) toward selenium dioxide in acetic acid. Because the product consisted of racemic carvomenthenol acetate (55,R=CH_3COO) these workers proposed that oxidation occurred through electrophilic attack by selenium dioxide on the double bond giving a symmetrical dipolar intermediate (56) which furnished a hyposelenite ester (55,R=OSeOH) by proton transfer; subsequent solvolysis by acetic acid then produced the observed racemic carvomenthenol acetate. Such a suggestion, however, besides ignoring the fact that carvomenthene may be racemised by acid alone, takes no account of the fact that such an electrophilic attack on an unsymmetrical compound should yield the product of complete allylic rearrangement, which is not in fact observed in the majority of cases.

Despite the lack of a concrete oxidation mechanism and the consequent difficulty of predicting products, the facile oxidation[62] of cedrene (57,R=H) to cedrenol acetate (57,R=CH_3COO) prompted investigation into the behaviour of the bicyclo(3,3,1)non-3-ene esters (19,R=CH_3; 25,R=CH_3,R'=H) towards selenium dioxide. Initially, to obtain reproducible conditions, the more available olefin ester (19,R=CH_3) was treated with selenium dioxide for varying periods in a

number of solvent systems, aqueous dioxan, aqueous ethanol acetic anhydride, acetic acid. Thus it was found that this olefin ester when heated under reflux for 1.5 hours with 1.1 equivalents of selenium dioxide in acetic acid was converted to an epimeric mixture of the corresponding allylic acetates (21,R=CH_3,R'=CH_3CO) whose infra-red spectrum was consistent with this assigned structure. This epimeric mixture of acetates was solvolysed to a mixture of hydroxy-esters (21,R=CH_3,R'=H) by treatment with anhydrous methanol containing a catalytic amount of sodium methoxide;[50] oxidation by means of chromium trioxide[63] furnished the keto-ester (20,R=CH_3), $\lambda_{max.}$= 229-230 mμ(8,250) which was catalytically reduced to the saturated keto-ester (22,R=CH_3). The homogeneity of the latter was confirmed by gas-liquid chromatography, and the position of the carbonyl function established by pyrazolone (23) formation on treatment with hydrazine.

These results taken together gave cause for considerable optimism, suggesting, as they did, that the desired allylic oxidation had been accomplished without allylic rearrangement. The homologous ester (25,R=CH_3, R'=H) when treated in identical fashion with selenium dioxide in acetic acid, furnished a solid product identified by infra-red spectrum and melting point as the lactone (46,R=H) previously obtained. Although the latter could be readily freed from accompanying allylic acetate by recrystallisation, an improved yield (78%) of the lactone resulted from hydrolysis of the crude oxidation product to mixture of the lactone (46,R=H) and the hydroxy-acid (25,R=H, R'=OH) followed by chemical separation

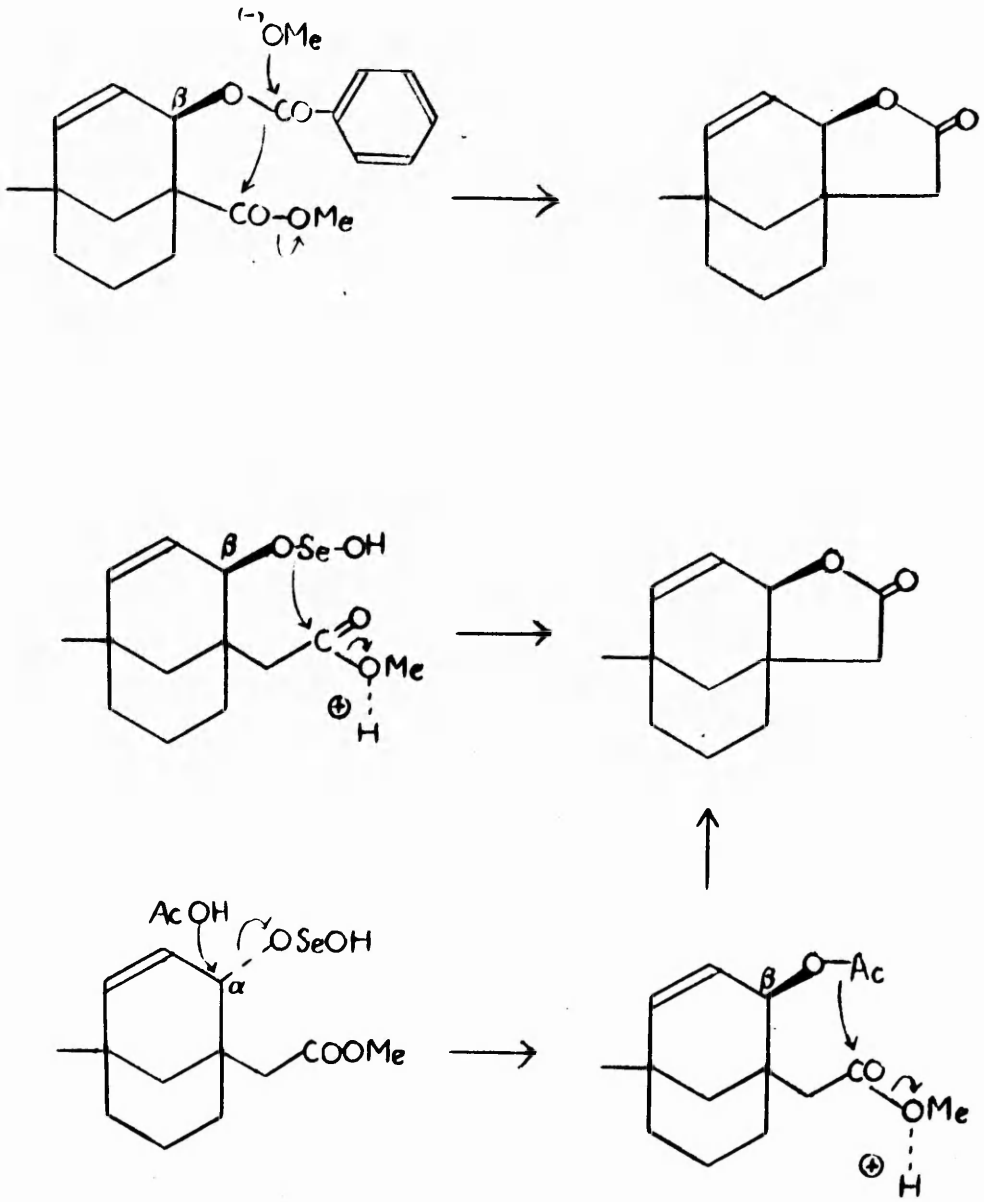


fig. 1

prior to recrystallisation of the lactone.

In view of the neighbouring group participation observed in the formation of the lactone by methanolysis[50] of the benzoyloxy-ester (25, R=CH_3, R'=C_6H_5COO), the direct formation of the lactone (46, R=H) by oxidation of the ester (25, R=CH_3, R'=H) in acetic acid was not unexpected. However, the high yield of homogeneous lactone and hence the apparent stereospecificity of the oxidation procedure must be reconciled with the fact that both α- and β- attack on the 2- methylene of the ester (25, R=CH_3, R'=H) appeared equally feasible. This seeming paradox may be resolved if the assumption is made that the first step in the oxidation is the formation of a hyposelenite ester (25, R=CH_3, R'=OSeOH) by attack of selenium dioxide followed by a hydrogen transfer of the type involved in the oxidation of hydrocarbons by chromium trioxide in acetic acid.[51] The fate of the hyposelenite ester (fig.1) is then dependent on the configuration at the C-2 position. Thus the 2β-epimer may lactonise directly by a nucleophilic attack on the protonated carbomethoxy group while the α-epimer may be solvolysed by the acetic acid with inversion at C-2 to the β-acetate which can cyclise by a similar nucleophilic attack. In each case selenium$^{\overline{IV}}$ has been converted to selenium$^{\overline{II}}$ which may be further reduced to metallic selenium in a subsequent allylic oxidation. Alternatively, one molecule of the oxidant may be simultaneously linked to two molecules of the olefinic ester (25, R=CH_3, R'=H) so that selenium$^{\overline{II}}$ species have only transient existence in the reaction medium.

The availability of the lactone (46,R=H) now permitted continuation of investigations which had been initiated to convert the lactone to the keto-acid (45,R=H) or the diketone (12, R=H). Since a trial hydrogenation of the lactone had revealed a susceptibility to hydrogenolysis, attempts to achieve opening of the lactone ring were carried out on the unsaturated lactone itself. In the first approach, conversion of the lactone to the hemi-acetal (58) of the keto-alcohol (26,R=OH) by reaction with one equivalent of ethylmagnesium bromide[64] was envisaged, but the lactone was recovered unchanged, even when excess reagent in refluxing tetrahydrofuran was employed.

The possibility was then considered of preparing the bromolactone (46,R=Br) which could conceivably be hydrolised to the unsaturated keto-acid (48,R=H). However, allylic bromination of the lactone with either N-bromosuccinimide or bromodan (N,N'-dibromodimethylhydantoin) afforded only starting material and an unidentified acid. In a similar approach oxidation of the lactone with potassium hypobromite gave a neutral material which decomposed over a period of months to a substance which was later identified as the required keto-acid (48,R=H).

In spite of this success, the final method adopted for the large-scale conversion of the lactone (46, R=H) to the keto-acid (48,R=H) was the following three-step procedure. Reduction of the lactone (46,R=H) by means of lithium aluminium hydride gave a quantitative yield of a sweet-smelling crystalline diol (59). However, oxidation

of this latter compound by commercial manganese dioxide in light petroleum gave, not the expected unsaturated keto-alcohol (62) but a quantitative recovery of the lactone. In view of the numerous examples of selective oxidation of allylic alcohols in the presence of other hydroxyl groupings,[34] this result was both surprising and disconcerting. Arigoni and his co-workers,[66] however, obtained a similar anomalous result in the oxidation of the sesquiterpene diol (60) which gave a keto-aldehyde on treatment with manganese dioxide, through attack on both hydroxyl functions. It was assumed, therefore, that the commercial manganese dioxide employed had been sufficiently active to oxidise the carbinol grouping to an aldehyde, permitting subsequent ring closure to a hemi-acetal (61). Further oxidation of the latter could then have furnished the lactone by a reaction of the type observed by Highet and Wildman[67] in the conversion of 2-hydroxytetrahydropyran to the corresponding γ-lactone by manganese dioxide.

Since a change of solvent in no way altered the course of oxidation, a sample of manganese dioxide was prepared according to the method of Attenburrow.[68] Oxidation of the diol (59) by the manganese dioxide thus prepared consistently gave the desired keto-alcohol (62) $\lambda_{max.}$ = 231-233 mμ (6,800) containing a small proportion of lactone and unoxidised diol. Further oxidation of the crude keto-alcohol (62) afforded the required acid (48,R=H) $\lambda_{max.}$ = 231-233 mμ (8,200) and a neutral fraction consisting of the lactone (46,R=H) and the keto-aldyhyde (62,R=H), which could be recycled to raise the overall yield in the conversion of the lactone to the acid

to 80%. The latter compound rapidly absorbed hydrogen, in the presence of palladised charcoal, to furnish the saturated keto-acid (45,R=H) m.p. 138-139°, the intermediate essential for construction of a tricyclic system by chain extension of the primary acid grouping.

Although the initial reaction had envisaged the acylation of cadmium diethyl[39] by the saturated keto-acid chloride as the obvious route to the diketone (12,R=H) and hence the tricyclic cyclopentenone (24,R=CH_3) the possibility had not been overlooked of preparing the latter from the enol-lactone (49). The reaction of δ-enol-lactones with methylmagnesium iodide has been employed to advantage[69,70] for the preparation of C-4 labelled cholest-4-en-3-one(64). From a study of this type of reaction Fujimoto[71] was able to show that Grignard reagents attacked the acyl portion of an enol-lactone (66) with simultaneous rearrangement of the acyl carbon atom to the β-olefinic carbon atom to form an intermediate bicyclo (3,3,1)nonane keto-alcohol (65). The keto-alcohol, under strongly basic conditions provided an excellent yield of the appropriate α,β-unsaturated ketone (64) without isolation of the intermediate diketone (67). The mechanism of the reaction was confirmed by studies on model compounds, and by the conversion of the enol-esters, isopropenyl acetate and vinyl acetate, to 2,4-dimethylpentan-2,4-diol and 3-methylheptan-3,5-diol by treatment with methylmagnesium iodide (2 moles) and ethylmagnesium bromide (2 moles).

Surprisingly, application of this method to the preparation of A-norcholestenone (68) from the γ-lactone (69) met with little

success. Jacobs and Takahashi[72] obtained no recognisable products from the reaction while Dauben and his colleagues[73] obtained a low yield (20%) of the intermediate bicyclo (3,2,1)octane keto-alcohol (70) whose structure was confirmed by infra-red, ultra-violet and N.M.R. spectroscopy. Prolonged treatment of this compound with strong base afforded a complex mixture containing a small proportion of A-norcholestenone (68) characterisable only through its 2,4-dinitrophenylhydrazone.

In the light of these results, the reaction of the γ-enol-lactone (49) with Grignard reagent was anticipated with no great optimism. In addition the low melting point, high solubility in organic solvents, and the consequent difficulty of purification by recrystallisation rendered the enol-lactone quite unsuitable as an intermediate. The substance did in fact appear to react with one equivalent of ethylmagnesium bromide but the product was sufficiently complex to discourage further reactions of this type.

Attention was then directed towards chain extension by the method developed in earlier work on the olefinic acid (25,R=R'=H) i.e. the acylation of cadmium diethyl. Preliminary investigations, however, showed that the product obtained by acylation with either the keto-acid chloride or its 'mixed' anhydride,[74] consisted entirely of the starting keto-acid (45,R=H) and the enol-lactone (49). The carbonyl group was therefore protected by ketalisation of the ester (45,R=CH_3) with ethylene glycol,[75] and the crystalline ketal-acid (71,R=OH) obtained by careful hydrolysis of the resulting ketal-ester (71,R=OCH_3). Unexpected difficulty was encountered in the

preparation of the required ketal-acid chloride (71,R=Cl); despite the use of oxalyl chloride and the sodium salt of the acid a multiplicity of peaks in the carbonyl region of the infra-red spectrum of the product cast considerable doubt on the homogeneity of the product. Since repeated attempts failed to provide a product with the expected single carbonyl absorption, the acid chloride (71,R=Cl) was added without purification to excess cadmium diethyl in benzene. After a prolonged reaction time, treatment with aqueous mineral acid and finally methanolic potassium hydroxide furnished mainly keto-acid (45,R=H) and a small neutral fraction (6%) identical in infra-red and ultra-violet spectra with the cyclopentenone (24,R=CH_3) obtained in previous work. The identity of the product was further corroborated by preparation of a red 2,4-dinitrophenylhydrazone, m.p. 223-225°, and by methylation, under conditions previously employed,[36] to clov-5-en-3-one (28). This latter product was developed as one spot on thin layer chromatography, but despite its apparent homogeneity a satisfactory analysis of distilled material could not be obtained, and the ketone could only be characterised through its infra-red spectrum and the crystalline 2,4,-dinitrophenylhydrazone.

At this stage, it was apparent that the abysmal yield (1%) in the conversion of the ketal-acid (71,R=OH) to clov-5-en-3-one (28), precluded the use of cadmium diethyl for the requisite chain extension. To satisfy the need for an alternative method of elaboration, attention was directed towards another class of organometallic compound, the organolithiums,[76] whose singular combination of high reactivity, ease of preparation, and solubility in inert

solvents, have encouraged their use in an ever-increasing number of reactions. Though primarily employed in place of Grignard reagents, organolithium compounds often offer substantial advantages and permit reactions which are unsuccessful with the former. In this case, the preparation of methyl ketones by the action of methyl-lithium on carboxylic acids, or their lithium salts,[79] was of particular relevance. Such a reaction was in fact first recognised by Gilman and van Ess during attempted carbonation of phenyl-lithium;[81] instead of benzoic acid, only benzophenone was obtained when the reaction was conducted at normal temperature. These workers proposed that the highly reactive phenyl-lithium attacked the initially formed lithium benzoate to form the dilithium salt of a dihydroxydiphenylmethane (72,R=Li) which afforded benzophenone by hydrolysis during the work-up. Gilman was able to extend the reaction to the preparation of several unsymmetrical ketones, and the scope of the reaction was illustrated by Tegner.[79] In addition, the latter established that the use of the free acid or its lithium salt exercised little effect on the yields of methyl ketones obtained from the cognate reaction between methyl-lithium and carboxylic acids.

The fact that negligible yields of the corresponding tertiary alcohols were observed in this reaction, was attributed to the formation of the stable dilithium salt (72,R=Li) resistant to further substitution or elimination of lithium oxide. From the reaction of phenyl-lithium on lithium benzoate Zook isolated a white, ether-insoluble solid, stable to heat in an inert atmosphere, but readily

hydrolysable to benzophenone and lithium hydroxide.[82] The analysis of the solid was consistent with the proposed structure (72,R=Li), but attempts to replace the lithium atoms by treatment with methyl iodide, ethyl bromide, and ethylene dibromide, invariably furnished benzophenone. It was assumed, therefore, that replacement of one lithium atom by an alkyl group afforded an unstable intermediate (72,R=alkyl) which lost lithium alkoxide before further substitution.

In view of the considerable information available on alkyl-lithiums,[76] it was felt that the appropriate diketone (12,R=H) might be obtainable via the action of ethyl-lithium on the ketal-acid (71,R=OH), although no example of the preparation of an ethyl ketone in this way had been encountered in the literature.

Ethyl-lithium is obtainable as a crystalline solid[80] m.p. 98°, but is most conveniently prepared in solution by careful addition of ethyl bromide to lithium wire in pentane.[77,78] By this method the ethyl-lithium is obtained as a violet suspension, contaminated with lithium bromide, in a saturated solution. If a product free of lithium bromide is required, the ethyl-lithium can be extracted by benzene and recrystallised. Alternatively, the ready displacement of mercury from diethylmercury by lithium metal, provides a convenient route to crystalline ethyl-lithium.[80]

Although both methyl-lithium and ethyl-lithium are crystalline solids and can be considered as homologous, the differences in their properties inevitably raised doubts as to the feasibility of the chain extension envisaged. Thus while methyl-lithium is normally prepared in ethereal solution by addition of methyl iodide to lithium

metal,[79] in the cognate preparation of ethyl-lithium only butane is produced (by Wurtz coupling[81] between ethyl iodide and ethyl-lithium). Furthermore, refluxing ether is itself decomposed by ethyl-lithium with formation of ethylene, ethane and lithium ethoxide,[76] and an inert solvent is therefore a prerequisite for the preparation of ethyl-lithium.

In a preliminary investigation, encouraging results were obtained from treatment of the ketal-acid (71,R=OH) with excess methyl-lithium, which furnished, in good yield, a colourless oil (71,R=CH_3) with carbonyl and ketal absorption in the infra-red spectrum, but no indication of a hydroxyl group. With ethyl-lithium, however, the ketal-acid furnished a neutral product (71,R=C_2H_5), displaying, in addition to that expected, absorption typical of a hydroxylic compound. The impurity was initially removed by chromatography but it was ultimately found that direct acid hydrolysis of the crude ketal-ketone (71,R=C_2H_5) gave the expected di-ketone (12,R=H) free of any hydroxylic material. It was concluded, therefore, that cleavage of the ketal ring by ethyl-lithium afforded the hemi-ketal (74,R=C_2H_5O) which was readily hydrolysed in acid to the diketone (12,R=H).

In one series of reactions, a sample of the diketone (12,R=H) thus obtained, furnished on chromatography a crystalline compound exhibiting hydroxyl, but not carbonyl, absorption in the infra-red; on the basis of analytical data the substance was assigned the tricyclic hemi-ketal structure (73).

Since the ketal-acid (71,R=OH) was not usually rigorously

purified before treatment with ethyl-lithium, it seemed probable that sufficient keto-acid (45,R=H) had been present to give a compound of this type by addition of ethyl-lithium to both the carboxyl and carbonyl functions, and cyclisation of the resultant hydroxy-ketone (74,R=C_2H_5).

Base catalysed cyclisation of the crude diketone (12,R=H) readily furnished the cyclopentenone (24,R=CH_3) $\lambda_{max.}$ 243-245 mμ, with extinction coefficient invariably greater than 10,000. Since the purest sample obtained showed an intensity of 14,600, purification by chromatography was carried out to obtain samples, which were homogeneous on thin layer chromatography, for further work.

The corresponding reaction between the ketal-acid (71,R=OH) and methyl-lithium presented no problems at the first stage, but the base treatment which had effected ring-closure of the ethyl analogue afforded a product with complex carbonyl absorption in the infra-red, and ultra-violet absorption at 237-238 mμ (5,700). It was finally realised, however, that prolonged base treatment was necessary to obtain the cyclopentenone (24,R=H) with extinction coefficient above 13,000.

At this stage in the synthesis, considerable encouragement was derived from a publication by Ringold and his co-workers[83] on conjugate anion formation and alkylation of Δ^4-3-keto steroids. Previously Yanagita[84] had been unable to explain the results of a study of methylation of the octalones (75,R=H; 75,R=CH_3). While treatment of the former ketone (75,R=H) with firstly potassium t-butoxide, then methyl iodide, readily afforded the 1,1-dimethyl

deconjugated ketone (76), under identical conditions the ketone (75,R=CH_3) was unreactive. Similar behaviour, observed in the steroid field,[85] stimulated investigation by Ringold and his colleagues into the methylation of 17α-methyltestosterone (77,R=H, R'=CH_3) and testosterone (77,R=R'=H), and their 4-methyl analogues (77,R=CH_3). It was found that the base treatment which led to the deconjugation of testosterone to (78,R=R'=H) left the 4-methyltestosterone (77,R'=H, R=CH_3) unchanged. Thus in base testosterone undergoes a rapid anion formation which may be followed by irreversible protonation by acetic acid to furnish the deconjugated ketone or methylation by methyl iodide to give the 4-methyl deconjugated ketone (78,R=CH_3, R'=H). Since the C-4 proton of the latter is more acidic than the C-6 proton of either testosterone or 4-methyltestosterone, under basic conditions rapid anion formation will occur, followed by either of two competing reactions: (i) methylation at C-4, which is favoured by the use of an excess of methyl iodide at low temperatures, or (ii) protonation at C-4, followed by double bond rearrangement, which can be encouraged by the use of a low concentration of methyl chloride, since the latter will hinder alkylation but leave the rate of protonation unaffected. Thus, by the appropriate choice of conditions, testosterone may be converted directly to Δ^5-4,4-dimethyltestosterone (78,R=R'CH_3) by a route which does not involve the unreactive 4-methyltestosterone (77,R=CH_3, R'=H) as an intermediate.[83]

These observations were of particular relevance at this stage of the synthetic approach, since similar behaviour in the C_{13} and C_{14}

cyclopentenones (24) would have made the former the more suitable precursor for clov-5-en-3-one (28). In fact, when the C_{13} ketone was treated with potassium t-butoxide, then methyl iodide, the desired clov-5-en-3-one was obtained in a yield appreciably greater than that enjoyed in monomethylation of the C_{14} compound.

Unfortunately, however, all attempts to saturate the double bond of the ketone (28) by catalytic hydrogenation were uniformly unsuccessful, and the C_{14} cyclopentenone (24,R=CH_3) once more assumed the role of key intermediate.

In a preliminary study, it was observed that the C_{13} ketone (24,R=H) absorbed hydrogen over palladium-charcoal very slowly; it was felt that the use of a more vigorous catalyst to accelerate the uptake might well induce hydrogenolysis of the ketone (24,R=CH_3) as in the reduction[86] of neotenulin (79) to desoxoneotenulin (80). The C_{14} compound was therefore reduced by lithium to liquid ammonia, and the resulting saturated alcohol re-oxidised to the ketone (81). Thin layer chromatography of the crude product revealed the presence of two fast travelling components, but after alumina chromatography the resulting low-melting solid was quite homogeneous on thin layer chromatography and gas-liquid chromatography. Since the Birch reduction had apparently furnished a sterically homogeneous product (after possible equilibration at C-4 induced by the alumina), it was now imperative that the nature of the ring fusion in the saturated ketone (81) be established, before further progress was made.

Although Barton[87] initially proposed that the product of metal-ammonia reduction of conjugated ketones was the thermodynamically

more stable one, Stork[88,89] later showed from a study of the reduction of octalones, that product stability was not a controlling factor; in fact, the steric course of reduction was governed by the relative stabilities of the cis (82) and trans (83) intermediate enolate anions which had the developing p-orbital of the β-carbon atom axial to the ketone ring. Thus the reduction of an octalone with lithium-ammonia gives the more stable of the cis and trans isomers having the newly introduced β-hydrogen atom axial to the ketone ring.[88] From an examination of the models of the enolate anions corresponding to the reduction of the C_{14} ketone (24, R=CH_3) it was concluded that the steric course of the Birch reduction was not predictable with any certainty. The cis conformer, however, possessed twol-3-diaxial interactions fewer than the corresponding trans conformer, when the bicyclononane nucleus was regarded as formed of two 'chairs'. In addition, only the cis conformer permitted the five-membered cyclopentene ring to adopt a strainless conformation, provided the adjacent cyclohexane ring of the bicyclo-(3,3,1)nonane system was allowed to adopt a boat conformation.

To establish the stereochemistry of ketone (81) unequivocally, the latter was condensed under basic conditions with furfural,[90] and the resulting crude product methylated directly; trituration of the dark oil obtained, afforded the furfurylidene derivative of the C_{15} ketone, $C_{20}H_{26}O_2$, (84) as a pale yellow crystalline solid, m.p. 108-109°; $\lambda_{max.}$ 333-335 mμ (22,000).

Ozonolysis of the latter followed by treatment with hydrogen peroxide in acetic acid provided only a neutral crystalline solid

possessing infra-red absorption at 1762, 1806 $cm.^{-1}$, typical of a glutaric anhydride. The product, after chromatography on silica and recrystallisation, melted at 76-78°, somewhat higher than the melting point, 50-51° of (-)-clovenic anhydride (85) prepared by oxidation of (-)-clovene (**1**). The infra-red spectra (carbon tetrachloride solution), however, were entirely superposable, and the two derived clovenic acids (86) exhibited the same melting point, undepressed on admixture. Clearly then, in the ketone (81) the cyclopentanone ring was fused in the required cis manner to the bicyclononane nucleus, and the reduction of the ketone (24,R=CH_3) had taken the desired course.

The availability of the ketone (81) stereochemically identical to clovene, laid the foundation for a final series of reactions which culminated in the synthesis of (±)-clovene. A trial methylation of the ketone by means of methyl iodide and 1.05 equivalent of sodium t-amylate[91] furnished a mixture of products, and the need for a 'blocking' group was clearly indicated. Of such groupings, the methylanilinomethylene group which had been used with considerable success,[53,92,93,94] appeared most likely to afford crystalline derivatives and was therefore the grouping of choice. Accordingly, the ketone (81) was condensed with ethyl formate in the presence of sodium methoxide, and the resulting alkali-soluble hydroxymethylene derivative (87,R=H) treated with 1.2 equivalents of N-methylaniline in either benzene or methanol, the latter providing slightly better yields.[53] The methylanilinomethylene derivative (88,R=H) was obtained as a dark oil which could not be induced to crystallise and

was therefore methylated directly, without further purification. Treatment with potassium t-butoxide for sixteen hours and methyl iodide for five hours afforded a dark red oil (88,R=CH_3) which, like its precursor, yielded no solid material. Since prolonged base hydrolysis[53] gave a product which still contained starting material, hydrolysis was accomplished by the two-stage procedure of Robinson.[92] The methylanilinomethylene derivative was firstly converted by means of hydrochloric acid to the hydroxymethylene derivative (87,R=CH_3) and the latter hydrolysed by strong alkali to clovan-3-one (89).

The overall yield, however, was only 20%, after chromatographic purification, and the infra-red spectrum of the product suggested that it consisted of mixture of clovanone and starting material (81). The methylation procedure was therefore repeated with sodamide in benzene in place of potassium t-butoxide in t-butanol. As before, the two stage hydrolysis furnished a poor yield of product, but the infra-red spectrum differed markedly from the starting ketone and analysis of the clovan-3-one (89) by gas-liquid chromatography revealed the presence of less than 5% of 4-desmethylclovan-3-one (81).

Repetition of this procedure on a larger scale, helped by the observation that clovan-3-one (89) was steam-volatile, provided a good yield (1.84g) of this vital ketone. Reduction of the pure material by means of lithium aluminium hydride furnished clovan-3-ol (90,R=H) as a crystalline mixture of epimers, m.p. 70-85°; the crude alcohol was esterified directly with ethyl chlorocarbonate and the absence of clovan-3-one (89) or clovan-3-ol (90,R=H) confirmed by thin layer chromatography of the resulting clovan-3-yl ethyl carbonate

(91). A portion of this ester was dissolved in silicone fluid and heated for four hours at 300°; the product was isolated by rapid distillation into a liquid nitrogen-cooled trap, freed of starting material by chromatography on alumina, and distilled under high vacuum to furnish a colourless, mobile oil identical in infra-red spectrum to authentic (-)-clovene. Treatment of the product with bromine in carbon tetrachloride[11] afforded a viscous dark oil which on trituration with ethanol yielded a crystalline diastereoisomeric mixture of racemic dibromides (92), m.p. 60-75°.

From this solid derivative very pure (±)-clovene was regenerated, by treatment with zinc dust in ethanol, as a colourless liquid indistinguishable (infra-red, N.M.R., mass spectra, and gas-liquid chromatography) from similarly regenerated (-)-clovene.[11]

During the early stages of the foregoing synthetic work, alternative routes to clovenic acid (86) received attention. Not the least attractive of such schemes involved a Michael reaction between 2-carbethoxy-6-methylcyclohexanone and the unsaturated aldehyde (95) to give the adduct (96). If the latter could have been obtained in this way, then cyclisation by means of concentrated sulphuric acid would have provided the ester (97), identical in carbon skeleton with clovenic acid. Although this route was ideal in principle, a number of inherent difficulties were unavoidable. Firstly, even if the required aldehyde (95) could be prepared, Michael addition to such a compound possessing a bulky substituent on the β-carbon atom is unfavourable.[95] Secondly, the steric course of this reaction was not predictable, and finally the cyclisation

of the adduct (96) would have been attended by the formation of rearrangement products of the type encountered during the cyclisation of the aldehyde (13).[26]

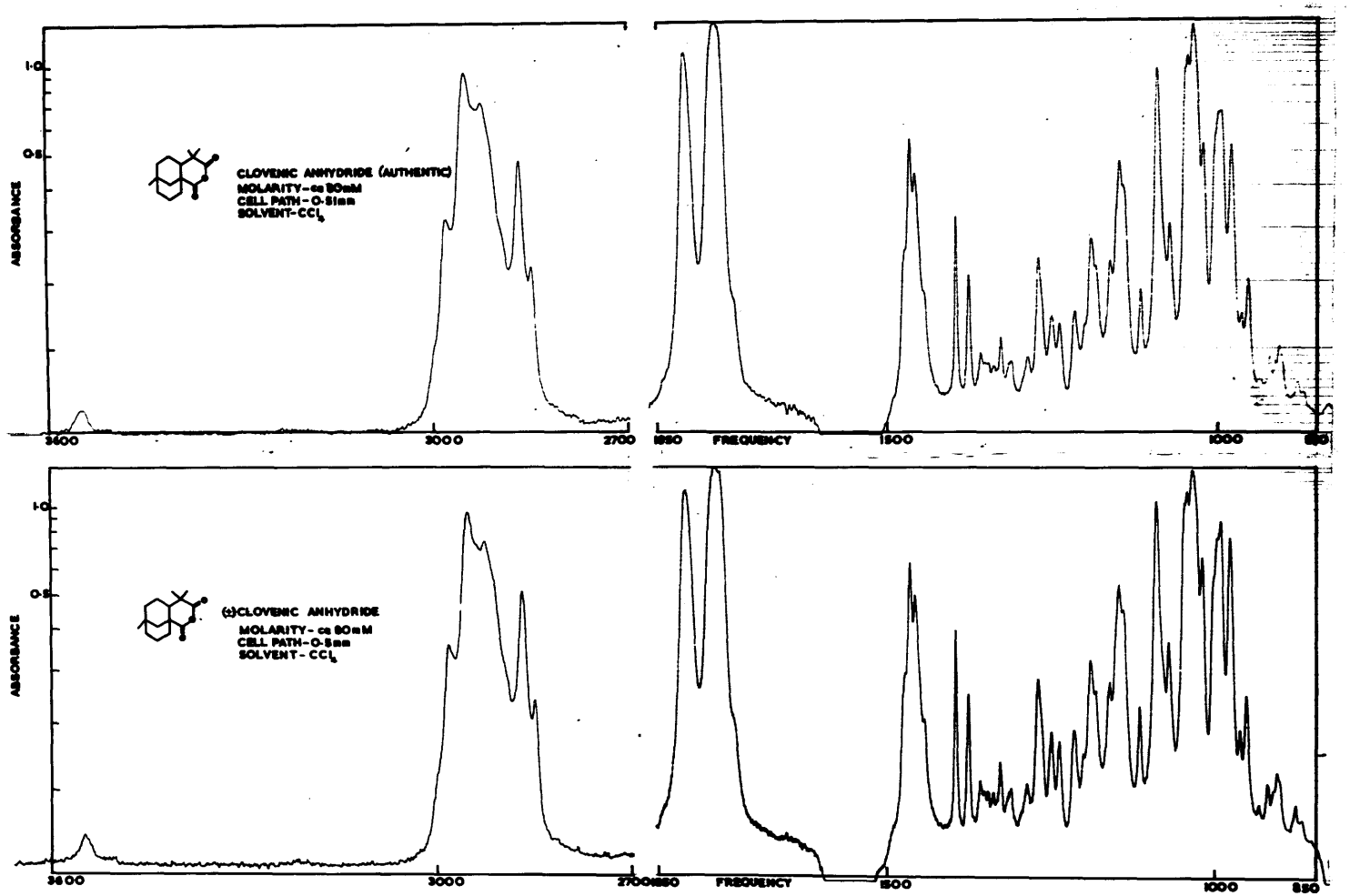
The desired aldehyde (95) was in fact prepared in poor yield by condensation of the aldehyde (94)[96] with ethyl vinyl ether[97] followed by hydrolysis of the intermediate acetal (98)[98] to a mixture of the starting aldehyde (94) and the unsaturated aldehyde (95), which was separated by fractional distillation. The corresponding reaction between the diethyl acetal of the aldehyde (94) and ethyl vinyl ether failed to yield the expected intermediate (99) which would have provided the desired aldehyde (95) on hydrolysis. In view of the successful applications of this latter type of reaction by Ogawa[98] and Nazarov[99] this result was both surprising and inconvenient, necessitating as it did the employment of the free aldehyde (94) for a condensation reaction which inevitably gave a mixture of starting material and product.[99]

Although the yield in the successful condensation was low, sufficient aldehyde (95), $\lambda_{max.}$ = 218-220 mμ (13,400) was available to permit a trial Michael reaction with 2-carbethoxy-6-methylcyclohexanone. Unfortunately, no base catalysed reaction could be induced between this β-keto-ester and the unsaturated aldehyde; at low temperature (-15°) no change was observed in the intensity of the absorption in the ultra-violet spectrum of the reaction mixture, and when the mixture was heated under reflux severe decomposition was evident.

In a second approach to clovenic acid (86) the terpene carvone

(102) was employed for the preparation of the keto-acid (101,R=H) by addition of formic acid[100] to the isopropenyl function of dihydrocarvone.[101] If the keto-ester(101,R=CH_3) were subjected to the annellation procedure[27] which had been employed for construction of the basic bicyclo(3,3,1)nonane skeleton viz. glyoxylation, Michael addition, and cyclisation, then the resultant bicyclo(3,3,1)nonane system (101) should have possessed the carbon framework of clovenic acid. Again, however, the projected synthesis was frustrated at the outset by a complete lack of success in the carboxylation of the double bond of dihydrocarvone.

After the successful synthesis of (±)-clovenic anhydride (85) attempts were made to effect an acyloin condensation on the methyl ester of clovenic acid. Reduction of the tricyclic keto-alcohols thus obtained, followed by treatment of the resultant diol (90,R=OH) with phosphorus diiodide[102] could have afforded the desired olefin clovene (1). In fact the required cyclisation was accomplished in low yield by means of a solution of sodium in liquid ammonia,[103] and only the successful conversion of the ketone (81) to clovan-3-one (89) interrupted a promising line of investigation.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CELL PATH - 0·5mm
SOLVENT - CCl4
ABSORBANCE
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3400
3000
2700
1650
FREQUENCY
1500
1000
850
(±)CLOVENIC ANHYDRIDE
MOLARITY - ca 80mM
CELL PATH - 0·5mm
SOLVENT - CCl4
ABSORBANCE
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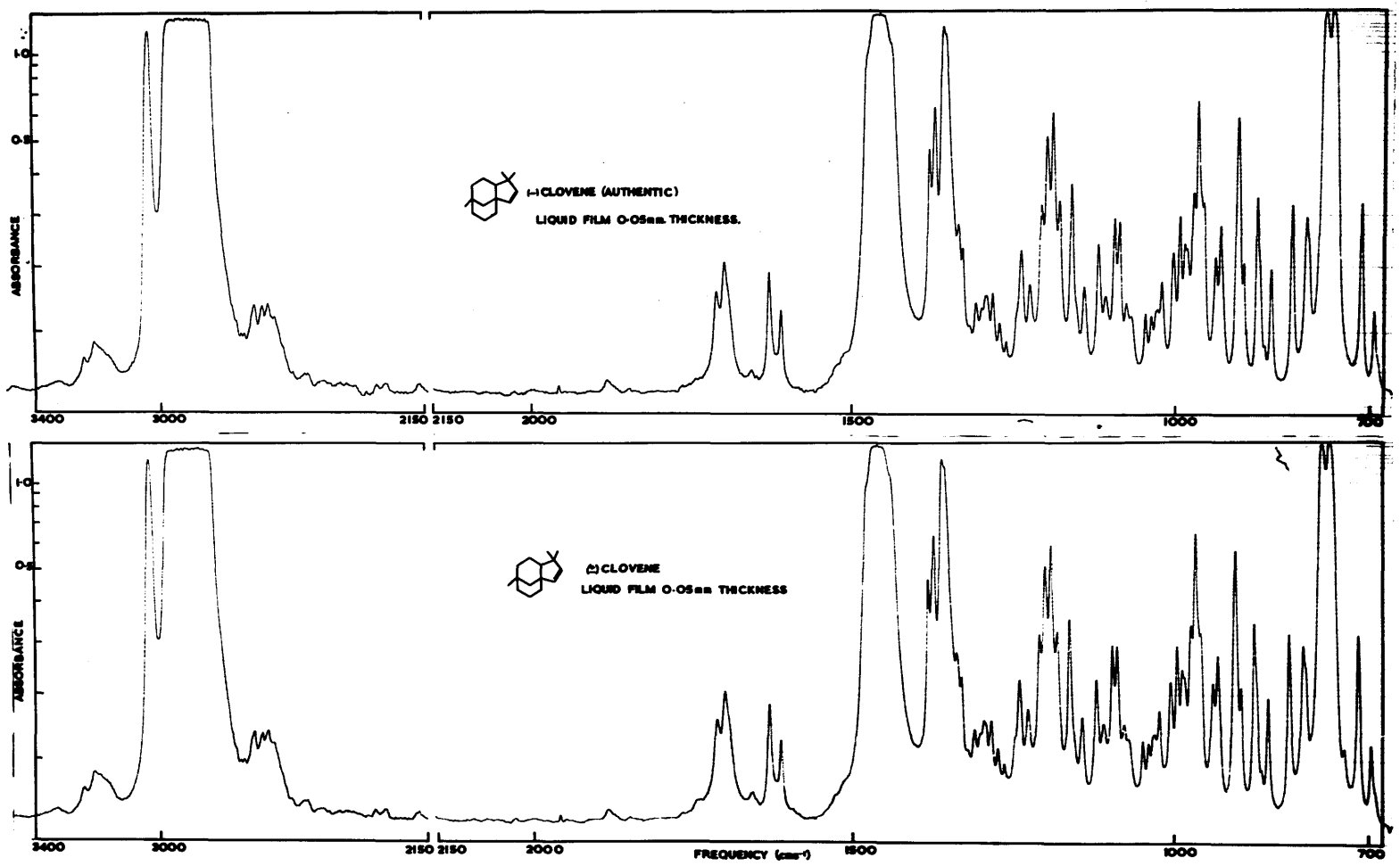
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LIQUID FILM 0·05mm. THICKNESS.
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ABSORBANCE
1·0
0·5
3400
3000
2150
2000
1500
1000
700
FREQUENCY (cm⁻¹)

EXPERIMENTAL

All melting points (corrected) were determined on a Kofler block; boiling points are uncorrected. Infra-red absorption spectra of liquid films and nujol mulls were recorded on a Perkin-Elmer Infracord spectro photometer, solution spectra on a Unicam S.P.100 spectrophotometer. Ultra-violet absorption spectra, measured on a Perkin-Elmer 137 U.V. spectrophotometer and a Unicam S.P. 500 spectrophotometer, refer to ethanol solutions. Mass spectra were determined on a Metropolitan-Vickers M.S.9 mass spectrometer, and N.M.R. spectra on the A.E.I. R.S.2 spectrometer.

The neutral alumina (Woelm) was used in the condition in which it was obtained from the suppliers, and for ordinary usage neutral alumina was prepared from Spence H alumina, and graded according to Brockmann and Schodder. Thin layer chromatography was carried out on silicagel G (Merck), and gas-liquid chromatography on a Pye 'Argon Chromatograph' with Celite 545 (120-150 mesh) acting as a support for Apiezon L stationary phase.

The term 'light petroleum' refers to the light petrol fraction b.p. 40-60°.

1-Carbomethoxy-5-methylbicyclo (3,3,1) non-3-ene (19, R=CH_3).

This ester (19,R=CH_3) was obtained as a sweet-smelling colourless liquid, b.p. 114°/20m.m., $\nu_{max.}$ = 3000, 1730, 1260, 710 cm. $^{-1}$, by the method of Murray, Parker, Raphael, and Jhaveri.[26]

Methyl 5-methylbicyclo (3,3,1) non-3-ene-1-acetate (25,R=CH_3,R=H).

(i) The olefin ester, 19, R=CH_3 (45.8g) was heated under reflux for four hours with a solution of potassium hydroxide (45g.) in methanol (450ml.). After removal of solvent, the residue was taken up in water, extracted once with ether, and acidified with dilute sulphuric acid (6N). Ether extraction (3 x 250 ml.), followed by brine washing, drying, and solvent removal furnished the olefin acid (19,R=H) as a white crystalline solid (40.5g.) which was employed without recrystallisation for the next stage.

(ii) Oxalyl chloride (19ml.) was added cautiously to a solution of the olefin acid, 19,R=CH_3, (30g.) in anhydrous benzene (300ml.) containing dimethylformamide (0.1ml.). When gaseous evolution had ceased (three hours), the solvent and successive portions (4 x 50ml.) were evaporated under reduced pressure to remove excess oxalyl chloride, leaving the acid chloride as a pale orange oil, $\nu_{max.}$ = 1785 $cm.^{-1}$ which was used for the next step without purification.

(iii) A solution of the acid chloride (32.9g.) in anhydrous ether (320ml.) was added to an ice-cold solution of diazomethane (Six equivalents) and the resultant yellow solution allowed to stand for four hours at room temperature. If necessary further treatment with diazomethane was carried out till the product showed no absorption in the infra-red at 1785 cm^{-1}. Removal of solvent gave the corresponding diazoketone as a yellow crystalline solid (32.3g.), $\nu_{max.}$ = 2100, 1620 cm^{-1}.

(iv) A saturated solution of silver benzoate in triethylamine (20ml.) was added portionwise, with stirring, to a solution of the diazoketone (32.3g.) in anhydrous methanol (600ml.). When the brisk exothermic, evolution of nitrogen (3.5l) had ceased (1.5 hours), ether (600 ml.) was added and the black precipitate of silver removed by filtration. After evaporation of the solvent, the residual dark oil was taken up in light petroleum and the resultant solution washed successively with dilute hydrochloric acid (1N), brine, aqueous sodium bicarbonate, brine, and dried over magnesium sulphate. Careful evaporation of solvent through a short Vigreux column yielded a yellow oil (31g.), $\nu_{max.}$ = 1770, 1730cm^{-1}. The crude material was adsorbed on alumina (grade H, 800g.) from light petroleum, and elution with this solvent (12 l.) gave a product (26g.) free of lactonic impurity. Fractional distillation afforded the homologated ester (25,R=CH_3,R^1=H) as a colourless, sweet-smelling oil (21.2g.), b.p. 84°/0.5m.m., $\nu_{max.}$ = 3000, 1730, 1260, 705cm.$^{-1}$

Attempted Wolff-Kishner reduction of the 9-keto-acid (14,R=H).

The keto-acid (2g.) was heated under reflux for 1.5 hours with a mixture of diethylene glycol (60ml.), ethylene glycol (15ml.), and hydrazine hydrate (100%, 4ml.). After the addition of a solution of sodium (2.5g.) in diethylene glycol (40ml.), the mixture was heated under reflux at 195° for four hours. The cooled mixture was poured onto ice-cold brine, acidified with dilute hydrochloric acid, and extracted with ether. The resultant product was found to consist of the crystalline pyrazolone (17) containing neither starting material nor the required 9-methylene acid (19, R=H).

Attempted homologation of the 9-keto-acid (14,R=H).

The 9-keto-acid (2g.) was subjected to the Arndt-Eistert procedure employed for the preparation of the ester (25,R=CH_3, R^1=H). The product (2.72g), however, was shown by thin layer chromatography to consist of at least six components. Chromatography on silica gave two main crystalline fractions, $\nu_{max.}$=1730, $\nu_{max.}$=1770, 1730cm.$^{-1}$; the former of these appeared to consist of the keto-ester (14,R=CH_3), and the latter a mixture of the same material and an unidentified lactonic product.

Methyl 2-benzoyloxy-5-methylbicyclo (3,3,1)non-3-ene-1-acetate (25,R=CH_3,R^1=C_6H_5COO).

t-Butyl perbenzoate (3.9g.) was added dropwise with stirring, over one hour to a suspension of cuprous bromide (0.2g.) in the ester, 25,R=CH_3, R=H, (3.9g.) held at 115° under nitrogen. The resulting blue mixture was stirred for a further hour before addition of ether (250ml.) and removal of unchanged cuprous bromide by filtration. The ethereal solution was washed with aqueous sodium carbonate solution to remove dissolved copper salts, brine, and dried over magnesium sulphate. After removal of solvent, the residual reddish oil (6.4g) was adsorbed on alumina (grade I, 120g.) from light petroleum and unchanged starting material (1.8g.) eluted with the same solvent. Further elution with benzene-light petroleum mixtures (1:9, 1:4, 1:1) afforded a partially solid mixture (3.1g.) of the epimeric benzoates (25,R=CH_3,R^1=H), $\nu_{max.}$ = 1730-1700, 1600, 1580cm^{-1}, which on recrystallisation from light petroleum (60-80°) furnished the β-epimer as glistening white

prisms: m.p. 91-92°. (Found: C,73.05; H, 7.55. $C_{20}H_{24}O_4$ requires C, 73.15; H, 7.35.)

Methanolysis of epimeric mixture of methyl 2-benzoyloxy-5-methylbicyclo (3,3,1) non-3-ene-1-acetate (25,R=CH_3,R^1=C_6H_5COO).

The mixture of benzoyloxy-esters (3.7g.) was heated under reflux with a solution of sodium (0.01g.) in anhydrous methanol (20ml.) for four hours. The cooled solution was neutralised with gaseous carbon dioxide and the methanol removed in vacuo. The residual oil (3.72g.) was adbsorbed on silica gel (100g.) from light petroleum and chromatographed. Elution with light petroleum and benzene served to elute methyl benzoate completely and further elution with benzene-chloroform mixtures (4:1, 1:1, 1:4) provided the lactone, 46,R=H,(1.84g.) of methyl 2-hydroxy-5-methyl bicyclo (3,3,1) non-3-ene-1-acetic acid (25, R=H, R^1=OH). Recrystallisation from light petroleum furnished white needles, m.p. 56-57°, $\nu_{max.}$ (CCl_4 soln.) = 1770 cm^{-1} (Found: C,75.15; H,8.70. $C_{12}H_{16}O_2$ requires C, 74.95; H, 8.40.)

Hydrolysis of methyl 2β-benzoyloxy-5-methylbicyclo (3,3,1) non-3-ene-1-acetate (25, R=CH_3, R=C_6H_5COO).

The crystalline benzoyloxy ester (0.663g.) in methanol (15ml.) containing potassium hydroxide (0.6g.) was heated under reflux for six hours. After evaporation of the methanol, the residue was dissolved in dilute brine and extracted with ether before acidification with dilute sulphuric acid (6N). The resultant mixture was extracted thoroughly

with ether and benzoic acid was removed with aqueous sodium bicarbonate solution. Further washing with brine, drying, and solvent removal yielded crystalline lactone, 46, R=H, (0.384g.). Acidification of the aqueous alkaline extracts furnished only benzoic acid.

Hydrolysis of mixture of epimeric benzoates (25,R=CH_3, R^1=C_6H_5COO).

The above procedure, applied to the mixture of epimeric benzoates (0.528g.), furnished a neutral fraction consisting of the crystalline lactone, 46, R=H, and an acidic brown oil (0.15g.) which on trituration with ether yielded small white crystals. Recrystallisation from ether gave a product m.p. 141-144°, $\nu_{max.}$ = 3300-2900, 3400, 1715, 705cm^{-1}, later shown to be 2α - hydroxy-5-methylbicyclo (3,3,1) non-3-ene-1-acetic acid (25, R=H, R^1=OH). (Found: C,68.55; H,8.40. $C_{12}H_{18}O_3$ requires C, 68.55; H,8.40.)

Attempted allylic oxidation of the ester (25,R=CH_3, R^1=H) using potassium chromate.

The ester (1.11g.) was heated under reflux with potassium chromate (2.9g.) in acetic acid (10ml.). At hourly intervals samples were withdrawn, diluted with water, and extracted with light petroleum. The ultra-violet spectra of the various fractions, however, showed no evidence of the presence of the keto-ester (48,R=CH_3) even after prolonged treatment.

Allylic oxidation using sodium dichromate dihydrate.

The olefinic ester, 25, R=CH_3,R^1=H, (0.87g.) was stirred for eight hours with a mixture of sodium dichromate dihydrate (2.15g.) and acetic

acid (5ml.) held at 85-100°. The cooled mixture was diluted with water and extracted thoroughly with light petroleum. The combined extracts were washed with brine, followed by aqueous sodium bicarbonate solution, and dried over magnesium sulphate. Solvent removal furnished a yellow oil (0.575g.), $\nu_{max.}$ = 1780 (γ-lactone), 1725, 1670cm.$^{-1}$, $\lambda_{max.}$=230-232mμ (3,400). The product was adsorbed on alumina (grade III, 20g.) from light petroleum and chromatographed. Elution with light petroleum afforded unchanged starting material and further elution with benzene-light petroleum provided a pale yellow oil (0.212g.), $\nu_{max.}$ = 1770, 1725, 1670 cm.$^{-1}$, $\lambda_{max.}$ = 230-232 mμ (5,100), consisting of the keto-ester (48,R=CH_3) containing a small proportion of lactonic material, later shown to be (46,R=H).

Allylic oxidation by means of anhydrous potassium chromate.

Anhydrous potassium chromate (5.4g.) was added to a solution of the olefinic ester 25, R=CH_3, R^1=H, (3g.) in glacial acetic acid (105ml.) and acetic anhydride (50ml.) containing benzene (1.1 ml.) held at 42°. The initial orange solution gradually became dark green through an intermediate brown stage over twenty-four hours. The cooled reaction mixture was added to a solution of sodium metabisulphite (6g.) in water (180ml.) and the resulting mixture thoroughly extracted with light petroleum. The combined extracts were washed repeatedly with a mixture of brine and aqueous sodium carbonate solution to remove the last traces of acetic anhydride and dried over magnesium sulphate. Removal of solvent gave a yellow oil (3.81g.) which was adsorbed on alumina (grade II, 100g.) from light petroleum and chromatographed. Elution with benzene-light

petroleum (3.2) gave an oil (0.575g.), $\lambda_{max.}$ = 230-232 mμ (2,000), and further elution with benzene-light petroleum (4.1) and benzene afforded a pale yellow liquid (1.14g.), $\lambda_{max.}$ = 231-232 mμ (6,900). The latter fraction on distillation furnished methyl 2-ketobicyclo (3,3,1) non-3-ene-1-acetate (48,R=CH_3) as a colourless oil (0.8g.), b.p. 94-96°/0.4m.m, $\lambda_{max.}$ =230-232 mμ (8,200).

Reactions of impure methyl 2-ketobicyclo (3,3,1) non-3-ene-1-acetate (48,R=CH_3) and its derivatives.

Hydrogenation of the mixture of keto-ester (48,R=CH_3) and lactone (46,R=H) from sodium dichromate oxidation.

The mixture (0.212g.) of keto-ester and lactone was shaken with palladium-charcoal (10%, 0.1g.) suspended in ethyl acetate (20ml.) till uptake of hydrogen had ceased (15ml., 65% of theoretical uptake). Filtration and concentration in vacuo furnished a colourless oil (0.196g.) which was heated under reflux for four hours with a solution of potassium hydroxide (0.2g.) in methanol (5ml.). After evaporation of methanol, the residue was acidified with dilute hydrochloric acid (6N) and extracted with ether. The organic material was separated into acidic and neutral components by extraction with aqueous sodium carbonate solution. The combined basic extracts were acidified and extracted with ether to give a pale yellow oil which could not be induced to crystallise. The neutral fraction of the extracts was found to consist of crystalline lactone (46,R=H), $\nu_{max.}$ = 1770 cm^{-1}, identical to that previously obtained.

Attempted enol-lactone and pseudo acid chloride formation.

(a) Non-crystalline keto-acid, 45, R=H, (0.15g.) was heated under reflux for eight hours with a solution of sodium acetate (0.02g.) in acetic anhydride (2 ml.). After concentration in vacuo, the residual viscous mixture was taken up in light petroleum and extracted repeatedly with aqueous sodium bicarbonate solution. The organic layer was dried over magnesium sulphate and concentrated in vacuo to furnish a dark oil which exhibited complex carbonyl absorption in the infra-red between 1700 and 1800cm^{-1} and could not be induced to yield any crystalline product.

(b) Oxalyl chloride (0.5 ml.) was added to a solution of the liquid keto-acid (0.2g.) in anhydrous benzene (5ml.). When gaseous evolution had ceased the excess of reagent was removed by repeated evaporation under reduced pressure with small volumes of solvent. The resultant crude acid chloride was warmed on the steam bath for twenty minutes with aluminium chloride (0.2g.). Addition of dilute hydrochloric acid (1N) followed by ether extraction and the customary brine washing and drying over magnesium sulphate yielded a viscous dark oil which was adsorbed on alumina from light petroleum and chromatographed. Elution with benzene and benzene-chloroform mixtures afforded small quantities of viscous material which failed to provide any of the expected crystalline pseudo acid chloride.

2-Keto-5-methylbicyclo (3,3,1) non-3-ene-1-acetic acid (48,R=H).

The keto-ester, 48,R=CH_3, (0.8g.), $\lambda_{max.}$=230-232 mμ (8,200) obtained by oxidation of the ester (25,R=CH_3, R^1=H) with anhydrous potassium chromate, was heated under reflux for four hours with a

solution of potassium hydroxide (0.7g.) in methanol (10ml.). After removal of methanol, the residue was taken up in dilute brine and extracted once with ether. The aqueous layer was acidified with dilute sulphuric acid (6N) and extracted thoroughly with ether. The combined extracts were washed with brine, dried over magnesium sulphate and concentrated in vacuo to give a partially solid product (0.744g.) which afforded the crystalline keto-acid, 48, R=H, (0.150g.) on trituration with ether. Sublimation at 140°, or recrystallisation from benzene furnished colourless prisms, m.p. 159-160°, $\nu_{max.}$ = 1720, 1630, 820 cm^{-1}. (Found: C, 69.15; H, 7.60. $C_{12}H_{16}O_3$ requires C, 69.20; H, 7.75).

2 α -Hydroxy-5-methylbicyclo (3,3,1) non-3-ene-1-acetic acid (25, R=H, R^1=OH).

The keto-ester, 48, R=CH_3, (0.120g.) was dissolved in methanol (2 ml.) and treated with a solution of sodium borohydride (0.02g.) in water (0.5 ml.) for three hours. The solution was acidified with dilute hydrochloric acid (6N) and extracted thoroughly with ether. The combined extracts were washed with aqueous sodium bicarbonate solution, brine, and dried over magnesium sulphate. Removal of solvent gave the expected hydroxy-ester (25, R=CH_3, R^1=OH) as a viscous oil (0.120g.) which was heated under reflux for four hours with a solution of potassium hydroxide (0.12g.) in methanol (2.4ml.). Acidification of the cooled solution, followed by ether extraction furnished a partially solid product which on recrystallisation proved to be identical in infra-red spectrum and melting point with the acid (25, R=H, R^1=OH) obtained by hydrolysis of methyl 2 α -benzoyloxy-5-methylbicyclo (3,3,1)

non-3-ene-1-acetate (25,R=CH_3,R^1=C_6H_5COO).

A sample (0.04g.) of the hydroxy-acid (25,R=H, R^1=OH) in acetone (2ml.) was treated with a solution (8N) of chromium trioxide in dilute sulphuric acid at 0° till a permanent red coloration persisted. The precipitated chromium salts were taken up in water and the mixture extracted thoroughly with ether. The etheral solution was washed with brine, dried over magnesium sulphate, and concentrated in vacuo to give a solid product (0.037g.) which on recrystallisation from benzene furnished a sample of the keto-acid (48,R=H) identical with that obtained from the potassium chromate oxidation.

2-Keto-5-methylbicyclo (3,3,1) nonane-1-acetic acid (45,R=H)

The crystalline keto-acid, 48, R=H, (0.111g.) rapidly absorbed the expected volume of hydrogen when shaken with a suspension of palladium-charcoal (10%, 0.05g.) in ethyl acetate (20ml.). Filtration and solvent removal furnished the expected keto acid (0.112g.) which on recrystallisation from benzene-light petroleum (1:1) afforded small white prisms m.p. 138-139°, $\nu_{max.}$ = 1720, 1670 cm^{-1}. Further small crops of crystalline material were obtained by seeding the products of hydrogenation, and then hydrolysis, of the crude keto-ester (48,R=CH_3) obtained from the various oxidation procedures. The structure of this keto-acid was unequivocally established at a later stage by its conversion to a crystalline enol-lactone (49), m.p. 32-34°. This latter derivative also confirmed that the correct structures had been assigned to the keto-acid (48,R=H), m.p. 159-160°, and the hydroxy-acid (25,R=H, R^1=OH), m.p. 141-144°.

Selenium Dioxide Oxidations.

(i) The olefin ester, 19, R=CH_3, (1.14g.) was heated under reflux for one hour with selenium dioxide (0.35g.) in aqueous dioxan (1:1, 10 ml.) and the product isolated by thorough extraction with light petroleum after removal of precipitated selenium by filtration. The material obtained, however, was identical in infra-red spectrum with the starting material, and even when the reaction time was extended to six hours no evidence of allylic oxidation was observed.

(ii) A similar result was obtained when the ester was heated under reflux for twelve hours with selenium dioxide (1.1 equivalents) in aqueous ethanol (1:1). The product isolated showed minimal hydroxyl absorption in the infra-red, despite the deposition of black selenium from the reaction mixture.

(iii) A solution of the olefin ester (1g.) in acetic anhydride (5 ml.) containing acetic acid (1 ml.) was heated on the steam bath for five hours with selenium dioxide (0.33g.). The cooled mixture was diluted with light petroleum (100 ml.), freed of selenium by filtration, extracted repeatedly with a mixture of brine and aqueous sodium bicarbonate, then concentrated in vacuo to give a dark orange oil (0.85g.) whose infra-red spectrum showed a displacement of the double bond absorption from 710 to 750 $cm.^{-1}$, suggesting that the desired allylic substitution had been accomplished.

(iv) When the ester (19,R=CH_3) was heated under reflux with selenium dioxide (1.1 equivalents) in acetic anhydride, black selenium was rapidly deposited. After two hours, the product was isolated,

according to the above procedure, as a dark red oil whose infra-red spectrum suggested strongly that although allylic oxidation had been effected, the conditions were rather severe.

(v) Finally, it was observed that the allylic oxidation was accomplished most efficiently when the ester (19, R=CH_3) was heated under reflux for ninety minutes with a suspension of selenium dioxide (1.1 equivalents) in acetic acid. Under these conditions, the product consisted of a pale orange oil which was partially decolorised when heated under gentle reflux for fifteen minutes with silver powder in benzene. The resultant sweet-smelling oil exhibited infra-red absorption which suggested that the olefin ester (19,R=CH_3) had been completely oxidised to the corresponding 2-acetoxy compound (21, R=CH_3, R^1=CH_3CO); thus the single carbonyl absorption at 1720cm^{-1} had been enhanced , the C-methyl absorption (1370cm^{-1}) had been enhanced, and the double bond absorption had been displaced from 710 to 750 $cm.^{-1}$

1-Carbomethoxy-2-keto-5-methylbicyclo (3,3,1) nonane (22,R=CH_3).

(a) The acetoxy ester, 21, R=CH_3, R^1=CH_3CO, (1.5g.) prepared as in (v) from the olefin ester, 19, R=CH_3, (1.38g.) was purified by chromatography on alumina (grade III, 30g.). Elution with benzene-light petroleum (1:1) furnished the desired diester (1.05g.) as an orange oil, $\nu_{max.}$=1720, 750cm^{-1}.

(b) Although the diester (21, R=CH_3, R^1=CH_3CO) could be converted in two steps to the corresponding hydroxy-ester (21, R=CH_3, R^1=H) by base hydrolysis followed by addition of diazomethane to the resultant hydroxy-acid (21, R=R^1=H), a direct conversion was more conveniently

achieved by methanolysis. Thus the diester (4.36g.) was heated under reflux with a catalytic quantity of sodium methoxide in methanol (50ml.). The cooled solution was neutralised with carbon dioxide and concentrated in vacuo to give the hydroxy-ester (21, R=CH_3, R^1=H) as a yellow oil, $\nu_{max.}$ = 3400, 1715, 1250, 750 cm^{-1}, which was adsorbed from light petroleum on silica and chromatographed. Elution with chloroform afforded an epimeric mixture (3.47g.) of the hydroxy-esters as a pale yellow oil.

(c) A solution (8N) of chromium trioxide in dilute sulphuric acid was added slowly to a solution of the hydroxy-ester, 21, R=CH_3, R^1=H, (3.47g.) in acetone (34.7 ml.) held at 0°, till a permanent red coloration persisted. The mixture was diluted with brine (10%, 150ml.) and the whole extracted thoroughly with light petroleum. The combined extracts were freed of acid and chromium salts by repeated washing with brine, dried over magnesium sulphate, and concentrated in vacuo to give the unsaturated keto-ester (20) as a pale yellow oil (3.21g.), $\nu_{max.}$ = 1720, 1650, 1250, 820cm^{-1}, $\lambda_{max.}$ = 229-230 mμ (8,250).

(d) The keto-ester, 20, (3.21g.) rapidly absorbed the expected volume of hydrogen when shaken with palladium-charcoal (10%, 0.64g.) in ethyl acetate (64 ml.). Filtration, followed by evaporation of solvent and distillation, afforded 1-carbomethoxy-2-keto-5-methylbicyclo (3,3,1) nonane (22) as a colourless liquid (2.89g.), b.p. 86-87°/0.15 m.m., $\nu_{max.}$=1720, 1685 cm^{-1}. A sample of the ester, subjected to analysis by gas-liquid chromatography was eluted as a single peak after seven minutes from an APL column (5%) at 175°.

With the homogeneity of the ester established, the structure (22) was confirmed by its conversion to a tricyclic crystalline pyrazolone (23). Thus the keto-ester, 22, (0.264g.) was heated under reflux for sixteen hours with a mixture of hydrazine hydrate (100%, 0.5ml.) and ethanol (1 ml.). After evaporation of solvent at the water pump, the residue was extracted with ether and the resultant solution washed thoroughly with a mixture of dilute hydrochloric acid (1N) and brine, followed by brine. By this procedure, the pyrazolone (23) was obtained as a white crystalline solid, which on recrystallisation from methanol afforded colourless plates indentical in melting point, 114-115°, and infra-red spectrum to the sample previously obtained.[24]

Allylic oxidation of methyl 5-methylbicyclo (3,3,1) non-3-ene-1-acetate (25, R=CH_3, R^1=H).

The homologated olefin ester (50g.) was heated under reflux for ninety minutes with a suspension of selenium dioxide (16.6.g) in glacial acetic acid (400 ml.). As soon as the mixture reached reflux temperature amorphous red selenium was precipitated but as oxidation took place the selenium gradually formed a black deposit on the walls of the reaction vessel. The resultant clear yellow solution was diluted with light petroleum (800 ml.) and filtered into dilute brine (10%, 1.6 l.). The product was thoroughly extracted with light petroleum (4 x 250 ml.) and the combined extracts washed thoroughly with brine, followed by aqueous sodium bicarbonate solution, dried over magnesium sulphate, and concentrated in vacuo to give an orange waxy solid (45g.) which on recrystallisation from light petroleum afforded the lactone (46,R=H)

as white needles (31.4g.). The mother liquors yielded a mixture (12g.) of the lactone and what was assumed to be the 2 α -acetoxy-ester (25, R=CH_3, R^1=CH_3COO) which was heated under reflux for four hours with a solution of potassium hydroxide (12g.) in methanol (200 ml.). After concentration in vacuo, followed by acidification, the resultant mixture of lactone and hydroxy-acid (25, R=R^1=H) was taken up in ether and separated by extraction of the acid with aqueous sodium bicarbonate solution to give a further quantity (5g.) of crude lactone. This material was adsorbed on silica from light petroleum and chromatographed; elution with chloroform-benzene (2:3) afforded a further quantity (3g.) of pure lactone (46, R=H).

Attempted ring opening of the lactone (46, R=H).

(i) When the lactone (0.100g.) was shaken with palladium-charcoal (10%, 0.02g.) in ethyl acetate, the uptake of hydrogen was extremely slow. The resultant product was found to consist principally of unchanged starting material, but a broad band in the infra-red at 2700-3300 cm^{-1} and the reduced intensity of the carbonyl absorption at 1770 cm^{-1} suggested that hydrogenolysis of the allylic oxygen function had preceded any hydrogenation.

Since the corresponding saturated lactone was unobtainable by this method, the lactone, 46, R=H, (0.100g.) was hydrolysed by treatment with a solution of potassium hydroxide (three equivalents) in methanol (5 ml.). The mixture was heated under reflux for four hours, concentrated in vacuo, and heated under gentle reflux for a further three hours with methyl iodide (2 ml.). Evaporation of solvent afforded a mixture of

lactone and the hydroxy-ester (25, R=CH_3, R^1=OH) which was taken up in light petroleum and chromatographed on silica. Elution with benzene-chloroform (3:2) afforded unchanged lactone, and further elution with chloroform furnished a small quantity (0.02g.) of the hydroxy-ester, $\nu_{max.}$ = 3400, 1715 cm^{-1}. The latter in acetone (0.5 ml.), was treated with a solution (8N) of chromium trioxide in dilute sulphuric acid but the product isolated consisted not of the desired keto-ester (48,R=CH_3) but of the lactone (46, R=H), formed by acid-catalysed cyclisation of the hydroxy-ester.

(ii) In an attempt to obtain the hydroxy-ketone (26, R=OH), the lactone (46, R=H) was treated with an ethereal solution of ethylmagnesium bromide (one equivalent) at 0° for one hour. The mixture was treated with an aqueous solution of ammonium chloride and extracted with ether. The resultant product, however, consisted entirely of unreacted starting material. The reaction was repeated, firstly by addition of the Grignard reagent to an ethereal solution of the lactone, maintained at reflux, and secondly by carrying out the entire reaction with tetrahydrofuran as solvent. In each case, however, the lactone was recovered quite unchanged.

(iii) Since it seemed probable that the bromolactone (46,R=Br) would be hydrolysed by base to the keto-acid (48, R=H) methods of allylic bromination were investigated. Thus N-bromosuccinimide (0.43g.) was added to a solution of the lactone, 46, R=H, (0.354g.) in carbon tetrachloride (15 ml.) containing a trace of dibenzoyl peroxide, and the mixture heated under reflux for fifteen minutes. The cooled solution was freed of succinimide by filtration and concentrated in

vacuo to give a viscous brown oil which fumed in moist air. The crude product was therefore heated under reflux for two hours with a solution of potassium hydroxide (0.5g.) in methanol (10 ml.). After evaporation of solvent, the residue was acidified with dilute sulphuric acid (6N) and extracted with ether. The resultant product (0.38g.), $\nu_{max.}$ =1770, 1630, 1700, 2700-3200 $cm.^{-1}$ was separated by chromatography on silica into the lactone, 46, R=H, (0.07g.) and an acidic component (0.25g.) whose ultra-violet spectrum, $\lambda_{max.}$ = 247-248 mμ , showed that it differed from the required keto-acid (48, R=H), $\lambda_{max.}$ =231-232 mμ (8,200).

(iv) Since the use of bromodan (N,N^1-dibromodimethylhydantoin) in place of N-bromosuccinimide brought about no improvement, a solution of the lactone (0.120g.) in aqueous ethanol (1:1, 1 ml.) was treated firstly with aqueous potassium hydroxide solution (33%, 0.5 ml.), then with bromine (0.11g.). When the solution had assumed a faint yellow coloration, the mixture was acidified with dilute sulphuric acid (6N) and the product extracted with ether. The combined extracts were washed with brine, dried over magnesium sulphate, and concentrated in vacuo to give a crystalline neutral product, insoluble in light petroleum and differing in infra-red absorption from the starting lactone (46, R=H). Recrystallisation from ether afforded colourless prisms which decomposed in the solvent at -10° over a period of months. The resultant brown mixture was taken up in ether, washed with brine containing a small quantity of sodium meta bisulphite, dried over magnesium sulphate and concentrated in vacuo to give a product identical in all respects to the keto-acid (48, R=H) previously obtained.

(v) Before this observation was made, however, ring opening of the lactone (46, R=H) had been achieved by means of lithium aluminium hydride. Thus the lactone (31.4g.) in anhydrous ether (125 ml.) was added dropwise to a suspension of lithium aluminium hydride (6g.) in ether (620 ml.) to maintain a gentle reflux which was continued for a further 2.5 hours before careful addition of wet ether, followed by dilute hydrochloric acid (6N). The resultant mixture was extracted thoroughly with ether, and the combined extracts washed repeatedly with brine, dried over magnesium sulphate, and concentrated in vacuo to give a viscous sweet-smelling oil (31g.) which on trituration with light petroleum furnished completely solid material. Recrystallisation from the latter solvent afforded the diol (59) as glistening prisms, m.p. 61-62°. (Found: C,73.40; H, 10.10. $C_{12}H_{20}O_2$ requires C, 73.45; H, 10.25.)

2-Keto-5-methylbicyclo (3,3,1) non-3-ene-1-acetic acid (48,R=H).

When the diol, 59, (0.09g.) was shaken for sixteen hours with a suspension of commercial manganese dioxide (1g.) in light petroleum (10 ml.) the product obtained by filtration, followed by evaporation of solvent, consisted entirely of the lactone (46, R=H), whose ultra-violet spectrum showed no maximum in the region 225-235 mμ . The oxidation was, therefore, repeated employing specially prepared oxidant. Thus the diol (31g.) was shaken with manganese dioxide (310g.) suspended in chloroform (2.5 .) for twenty hours to give the desired keto-alcohol, 62, (31g.) contaminated with some lactone (46, R=H) and unchanged diol (59). Recrystallisation from light petroleum furnished the keto-alcohol

(62) as colourless prisms m.p. 45-47°, $\nu_{max.}$ = 3400, 1650, 820 cm^{-1}, $\lambda_{max.}$ = 231-232 mμ(8,200). (Found: C,74.10; H, 9.40 $C_{12}H_{18}O_2$ requires C,74.20; H, 9.35.)

Oxidation of the keto-alcohol (62) to the desired keto-acid (48,R=H) was accomplished by dropwise addition of a solution (8N) of chromium trioxide in dilute sulphuric acid to a solution of the keto-alcohol (31g.) in acetone (310 ml.), maintained at 0°, till a permanent red coloration persisted. After 1.5 hours, brine (500 ml.) was added to the mixture and the acetone carefully evaporated under reduced pressure before thorough ether extraction. The combined extracts were washed with brine till colourless, and the keto-acid thoroughly extracted with aqueous sodium bicarbonate solution. The aqueous layer was then acidified with dilute sulphuric acid (6N) and extracted with ether to give white crystalline keto-acid, 48, R=H, (20.3g.). The initial ether extracts, on evaporation afforded the neutral component (10.7g.) which appeared to consist of a mixture of the lactone (46,R=H) and the aldehyde (63,R=H). This neutral fraction was combined with the crude lactone (3g.) obtained from the mother liquors of the initial recrystallisation of the lactone, and reduced as before to the diol (59). Two stage oxidation again furnished a further quantity (6.9g.) of the keto-acid (48, R=H) and the expected neutral fraction which was recycled. In this way, the lactone (34g.), obtained by oxidation of the ester 25, R=CH_3, R^1=H, (50g.), was converted to the keto-acid, 48, R=H, (30g.) in a yield of 80%.

2-Keto-5-methylbicyclo (3,3,1) nonane-1-acetic acid (45,R=H) .

The keto-acid, 48, R=H, (4.72g.) rapidly absorbed hydrogen when shaken with palladium-charcoal (10%, 0.472g.) in ethyl acetate (100 ml.). The keto-acid (45, R=H) was obtained by filtration, followed by removal of solvent as a white solid (4.73g.) which on recrystallisation from benzene furnished colourless prisms, m.p. 138-139°, $\nu_{max.}$ = 1720, 1670 cm^{-1} (Found: C, 68.85; H, 8.45. $C_{12}H_{18}O_3$ requires C, 68.55; H, 8.65.)

The enol-lactone (49) of the keto-acid (45,R=H) .

The keto-acid (1.6g.) was heated under reflux for twenty hours with a solution of sodium acetate (0.16g.) in acetic anhydride (24 ml.). After evaporation of the solvent under reduced pressure, the residue was taken up in ether and the resultant solution washed thoroughly with aqueous sodium bicarbonate solution and finally brine. The ethereal solution was dried over magnesium sulphate and concentrated in vacuo to furnish a dark oil (1.5g.) which was adsorbed on alumina (Woelm grade I, 16g.) from light petroleum and chromatographed. Elution with light petroleum afforded the enol-lactone (49) as a pale yellow solid (1.06g.) which on recrystallisation from pentane yielded large translucent plates m.p. 32-34°, $\nu_{max.}$ = 1800, 1700 cm^{-1} (Found: C,74.75; H, 8.10, $C_{12}H_{16}O_2$ requires C, 74.95; H, 8.40.)

The infra-red spectrum of the compound was unusual in respect of the intensity of the double bond at 1700 cm^{-1} and the number of high intensity absorption peaks between 1400 and 800 cm^{-1}.

The enol-lactone (49) was readily hydrolysed by treatment with a solution of potassium hydroxide (three equivalents) in methanol on the steam bath for thirty minutes. Acidification of the cooled solution followed by extraction with ether provided a quantitave yield of a crystalline product identical in all respects to the keto-acid (45,R=H).

2,2-Ethylenedioxy-5-methylbicyclo (3,3,1) nonane-1-acetic acid (71,R=OH).

The keto-ester (45,R=CH_3) was obtained as a colourless oil by the addition of an ethereal solution of diazomethane to the keto-acid (45, R=H). Ketalisation was accomplished by heating a mixture of the keto-ester (5.0g.), ethylene glycol (7.8 ml.), ethyl orthoformate (15.6 ml.), and p-toluenesulphonic acid (0.05g.), at 165° for two hours. The resultant pale yellow solution was taken up in light petroleum, washed twice with brine (20%), dried over magnesium sulphate, and concentrated in vacuo to give the ketal-ester (71, R=CH_3O) as a yellow oil, which distilled as a colourless liquid (5g.), b.p. 109-110°/0.17 m.m., $\nu_{max.}$ = 1725, 1200-1100 cm^{-1}. (Found: C,66.90; H, 8.45. $C_{15}H_{24}O_4$ requires C, 67.15; H,9.00.).

The ketal-ester (5g.) was heated under reflux with an aqueous solution of sodium hydroxide (1N, 60 ml.) till complete dissolution had occurred. The cooled solution was carefully acidified at 0° with standard hydrochloric acid (1N, 60 ml.) and then extracted thoroughly with ether. The combined extracts were dried over magnessium sulphate and concentrated in vacuo to give the ketal-acid (71, R=OH) as a viscous oil (4.72g.) which solidified on standing. Recrystallisation from light petroleum furnished small prisms, m.p.80-83° (Found:C,66.15, H.8.90 $C_{14}H_{22}O_4$ requires C, 66.10; H, 8.70.)

Diethylcadmium.

An ethereal solution of ethylmagnesium bromide was prepared by addition of an ethereal solution of ethyl bromide (1.5 equivalents) to a suspension of magnesium turnings (1 equivalent) in a small volume of ether under nitrogen. When the initial vigorous reaction had subsided, the solution was heated under reflux till the last traces of magnesium had dissolved. The solution was then cooled to 0° and anhydrous cadmium chloride (2 equivalents) added carefully in small portions. The mixture was stirred for one hour at room temperature and then heated under reflux for thirty minutes to complete the formation of diethylcadmium. The mixture was evaporated to small volume and the residue diluted with anhydrous benzene. Repeated distillation to small bulk and addition of portions of benzene served to remove the last traces of ether, and give a solution of diethylcadmium in benzene.

Preparation of 1-(2-ketobutyl)-2-keto-5-methylbicyclo (3,3,1) nonane (12, R=H) by the acylation of diethylcadmium.

(a) The acid chloride of the keto-acid (45,R=H) was prepared by addition of oxalyl chloride (1 ml.) to a solution of the acid (0.270g.) in benzene (10 ml.) containing a trace of dimethylformamide. When the evolution of gaseous products had ceased (three hours), the solvent was removed and excess reagent eliminated by repeated evaporation of the solution to small volume with portions (5 ml.) of benzene. The acid chloride was thus obtained as a viscous yellow oil, $\nu_{max.}$ = 1800, 1700 cm^{-1}.

A solution of the acid chloride in benzene (5 ml.) was added dropwise with stirring to a solution of diethylcadmium (prepared from magnesium, 0.150g.) in benzene. Stirring was continued for four hours at room temperature before addition of a mixture of ice-cold brine and dilute hydrochloric acid. The mixture was extracted thoroughly with ether, and the combined extracts washed with brine, dried over magnesium sulphate, and concentrated in vacuo to give a pale yellow oil (0.273g.) which was adsorbed on alumina (grade III, 5g.) from light petroleum and chromatographed. Elution with light petroleum afforded a colourless oil (0.05g.), $\nu_{max.}$ = 1800, 1700 cm^{-1}, identical in infra-red spectrum to the enol-lactone (49), and further elution with chloroform yielded the starting keto-acid, 45, R=H, (0.08g.).

(b) The 'mixed' anhydride (45, R=C_2H_5OCO) of the keto-acid (45,R=H) with carbonic acid was prepared by addition of ethyl chloroformate (0.362g.) in benzene (10 ml.) to a solution of the keto-acid (0.700g.) in benzene (5 ml.) and triethylamine at 0°. After forty-five minutes, the precipitated triethylamine hydrochloride was removed by filtration and the resultant clear solution added dropwise with stirring to a solution of diethylcadmium (prepared from magnesium, 0.320g.) in benzene under nitrogen. The mixture was stirred for sixteen hours at room temperature and the product isolated by the method described above. The neutral material obtained (0.570g.) consisted, as before, of the enol-lactone (49) which was hydrolysed by aqueous potassium hydroxide solution to the starting keto-acid (45, R=H).

(c) The ketal-acid chloride (71, R=Cl) was prepared by addition of oxalyl chloride (3.7 ml.) to a suspension of the anhydrous sodium salt

of the ketal-acid, 71, R=OH, (4.72g.) in benzene (50 ml.). After two hours the precipitated sodium chloride was removed by filtration and the resultant clear solution concentrated in vacuo to give a viscous yellow oil (5g.), $\nu_{max.}$ = 1700-1800 cm^{-1}. The crude acid chloride (71, R=Cl) in benzene (75 ml.)was added with stirring over fifteen minutes to a solution of diethylcadmium (prepared from magnesium, 1.3g.) in benzene, under nitrogen. The mixture was stirred for a further sixteen hours, and the product isolated as before. To isolate the required diketone (12, R=H) the crude product (4.3g.) was heated under reflux for two hours with aqueous acetic acid (1:1, 50 ml.) containing hydrochloric acid (6N, 1 ml.). The cooled solution was diluted with brine (10%, 200 ml.) and extracted with ether. The combined extracts were washed with dilute brine (10%) and recovered keto-acid (45, R=H) extracted with aqueous sodium bicarbonate solution. Acidification of the aqueous alkaline layer, followed by extraction with ether in fact afforded a large proportion (2.47 g.) of the keto-acid (45, R=H). The neutral component (1.45g.) consisted of a yellow oil, $\nu_{max.}$ = 1700, 1730 $cm.^{-1}$; a portion (1g.) of this material was heated under reflux for three hours with a solution of potassium hydroxide (1g.) in methanol (20 ml.) to effect cyclisation of any diketone (12, R=H) present. After removal of methanol, the residue was taken up in a mixture of brine (10%) and ether, and separated. The aqueous layer, on acidification and extraction with ether, afforded a further quantity (0.528g.) of the keto-acid (45,R=H) while the ethereal solution furnished a neutral sweet smelling oil (0.21g.) $\nu_{max.}$=1630, 1710 $cm.^{-1}$, $\lambda_{max.}$ = 243-245 mμ (10,000). This latter material was chromatographed on alumina (grade H, 4g.) to give a number

of fractions $\lambda_{max.}$ = 243-245 mμ (12,000-14,600). The oil was identified as 4-desmethylclov-4-en-3-one (24, R=CH_3) by preparation of a deep red 2,4-dinitrophenylhydrazone, identical in melting point and mixed melting point, 223-225°, to that obtained from the tricyclic cyclopentenone (24, R=CH_3) in earlier work.

Clov-5-en-3-one (28).

The conjugated ketone, 24, R=CH_3, (0.060g.) was heated under reflux for one hour with a suspension of potassium t-butoxide (0.10g.) in benzene (10 ml.) in an atmosphere of nitrogen. A solution of methyl iodide (1 ml.) in benzene (5 ml.) was added to the cooled mixture and the whole heated under gentle reflux for a further hour. The mixture was then poured onto ice-cold brine and extracted with light petroleum. The product obtained consisted of a dark oil (0.062g.), $\nu_{max.}$ =1740, 1700, 1630 $cm.^{-1}$, $\lambda_{max.}$ = 243-245 mμ (3,000). Careful chromatography on alumina (Woelm grade I, 2g.) furnished the C_{15} ketone (28) as a colourless oil (0.012g.), $\nu_{max.}$ = 1740, 1385, 1365 $cm.^{-1}$, which was developed as a single spot on thin layer chromatography. A less pure sample (0.022g.) was employed for the preparation of the orange 2,4-dinitrophenylhydrazone, identical in melting point and mixed melting point, 156-158°, with that obtained in previous investigations.

Addition of methyl-lithium to the ketal-acid (71, R=OH).

An ethereal solution of methyl-lithium was prepared by dropwise addition of a solution of methyl iodide (3 ml.) in ether (25 ml.) to a well-stirred suspension of finely divided lithium (0.58g.) in ether (25 ml.) under nitrogen, at a rate sufficient to maintain a gentle

reflux. The mixture was heated under reflux for a further two hours to complete the dissolution of the lithium, and the cooled solution was filtered into a solution of the ketal-acid (2.84g.) in ether (28.4g.) maintained at gentle reflux. The opaque white mixture was heated under reflux for two hours and the lithium complex cautiously decomposed by the addition of ice-cold brine (40 ml.) to the cooled solution. The mixture was thoroughly extracted with light petroleum and the combined extracts washed with brine. The aqueous alkaline layer on acidification and ether extraction, provided a high proportion (1.6g.) of unreacted ketal-acid (71, R=OH), while the original light petroleum solution afforded a colourless oil (1.4g.), consistent in infra-red absorption, $\nu_{max.}$ = 1710, 1200-900 $cm.^{-1}$, with the expected product (71,R=CH_3).

1-Acetonyl-2-keto-5-methylbicyclo (3,3,1) nonane (93).

The ketone, 71, R=CH_3, (1.0g.) was heated under reflux for three hours with a solution of hydrochloric acid (6N, 0.1 ml.) in aqueous methanol (1:1, 10 ml.). The cooled reaction mixture was diluted with brine (20 ml.) and extracted with light petroleum (3 x 25 ml.). The combined extracts were washed with brine, dried over magnesium sulphate and concentrated in vacuo to give the diketone (93) as a yellow oil (0.827g.), $\nu_{max.}$ = 1710 $cm.^{-1}$, which was developed as one main spot, with four minor impurities, on thin layer chromatography. A sample (0.6g.) of the crude material was adsorbed on alumina (grade III, 16g.) from light petroleum and chromatographed. Elution with the same solvent afforded the diketone (93) as a colourless oil (0.250g.) which was homogeneous on thin layer chromatography.

Cyclisation of the diketone (93) to the tricyclic ketone (24, R=H).

The diketone (0.250g.) was heated under reflux for sixteen hours with a solution of potassium hydroxide (0.4g.) in methanol (5 ml.). The cooled solution was diluted with brine and extracted with light petroleum. The combined extracts were dried over magnesium sulphate and concentrated in vacuo to give the desired cyclopentenone (24, R=H) as a yellow oil (0.184g.), $\nu_{max.}$ = 1690, 1630 cm^{-1}, $\lambda_{max.}$ = 237-238 mμ (12,700).

Clov-5-en-3-one (28).

The tricyclic ketone, 24, R=H, (0.180g.) was heated under reflux for one hour with a suspension of potassium t-butoxide (0.500g.) in benzene (10 ml.) in an atmosphere of nitrogen. Methyl iodide (2 ml.) was added to the cooled solution and the mixture heated under gentle reflux for a further two hours. The mixture was treated with ice-cold brine (20 ml.) and extracted with light petroleum. The crude material (0.168g.) thus obtained was adsorbed on alumina (Woelm grade I, 5g.) from light petroleum. Elution with the same solvent furnished a colourless oil (0.100g.) $\nu_{max.}$ = 1740, 1385, 1365 cm^{-1}, which was developed as a single spot on thin layer chromatography, and readily gave the same orange 2,4-dinitrophenylhydrazone as that obtained from the sample of clov-5-en-3-one prepared in low yield by the acylation of diethylcadmium.

Addition of ethyl-lithium to the ketal-acid (71,R=OH).

A violet solution of ethyl-lithium in pentane was prepared by slow, regular addition with stirring, over four hours, of a solution of ethyl bromide (40g.) in pentane (150 ml.) to lithium wire (6g.) in pentane

(100 ml.) maintained at gentle reflux in an inert atmosphere under a mercury seal. After one hour the lithium metal assumed a purple coloration while the solvent gradually became cloudy as a result of the formation of lithium bromide and violet ethyl-lithium. After five hours the solution and suspension were decanted and added rapidly to a solution of the ketal-acid (11.6g.) in pentane (116 ml.). When the addition had been completed, the mixture was heated under reflux and stirred for two hours. After careful addition of ethanol to destroy excess ethyl-lithium, the mixture was diluted with ice-cold brine (100 ml.) and the product extracted with light petroleum. The neutral material (71, R=C_2H_5) consisted of a pale yellow oil, $\nu_{max.}$=3400, 1710, 1200-900 $cm.^{-1}$ containing a hydroxylic impurity. The aqueous alkaline layer, furnished on careful acidification, followed by extraction with ether, some unreacted ketal;acid (71, R=OH) which was recycled to give a high yield (11.6g.) of the desired ketone (71, R=C_2H_5). A sample (1.3g.) was adsorbed on alumina (grade H, 30g.) from light petroleum and chromatographed; elution with the same solvent afforded the ketal-ketone as a colourless oil, b.p. 104°/0.07m.m., $\nu_{max.}$ = 1710, 1200-900 $cm.^{-1}$, which was shown to be homogeneous by this layer chromatography. (Found: C, 72.05; H, 9.55. $C_{16}H_{26}O_3$ requires C,72.15; H, 9.85.).

1-(2-Ketobutyl)-2-keto-5-methylbicyclo (3,3,1) nonane (12,R=H).

The ketal-ketone 71, R=C_2H_5, (9.9g.) was heated under reflux for three hours with a solution of hydrochloric acid (6N, 0.5 ml.) in aqueous methanol (1:1, 250 ml.). As hydrolysis proceeded the two-phase mixture gave way to a pale yellow solution which was diluted with

ice-cold brine (500 ml.) and extracted thoroughly with light petroleum. The diketone (12, R=H) was obtained as a yellow oil (8.2g.), $\nu_{max.}$ = 1710 $cm.^{-1}$, apparently free of the hydroxylic impurity observed in its precursor (71, R=C_2H_5). A sample (0.6g.) of the crude material was adsorbed on silica (20g.) from light petroleum and chromatographed; elution with ether-light petroleum (1:19) afforded a solid product, which recrystallised from light petroleum as fine needles, m.p. 95-100°, $\nu_{max.}$ = 3450 $cm.^{-1}$ (Found: C,76.10; H,11.25. $C_{16}H_{28}O_2$ requires C,76.15; H,11.20). Further elution with ether-light petroleum afforded the desired diketone (12, R=H) as a pale yellow oil which distilled as a colourless liquid b.p. 100°/0.12 m.m., $\nu_{max.}$ = 1710 $cm.^{-1}$ (Found: C,75.70; H, 10.00. $C_{14}H_{22}O_2$ requires C, 75.65; H, 9.95.).

4-Desmethylclov-4-en-3-one (24, R=CH_3).

The diketone, 12, R=H, (7.6g.) was heated under reflux for three hours with a solution of potassium hydroxide (8g.) in methanol (120 ml.). The cooled solution was diluted with brine (250 ml.) and extracted with light petroleum. The combined extracts were washed with brine, dried over magnesium sulphate, and concentrated in vacuo, to give a sweet-smelling yellow oil (7.37g.), $\nu_{max.}$ = 1690, 1630 $cm.^{-1}$, $\lambda_{max.}$ =242-244 mμ (11,000). The crude material was adsorbed on alumina (grade H,180g.) from light petroleum and chromatographed.

Elution with ether-light petroleum (1:9, 1:4, 1:1) afforded a pale yellow oil (4.167g.), homogeneous on thin layer chromatography, which on distillation furnished the desired ketone (24, R=CH_3) as a colourless

liquid, b.p. 74-76°/0.05m.m., $\lambda_{max.}$ = 243-245 mμ (12,800).
(Found: C, 81.80; H, 9.60. $C_{14}H_{20}O$ requires C, 82.30; H, 9.85.)

As was observed in the earlier work, methylation of this product afforded the C_{15} ketone (28) in low yield.

Attempted hydrogenation of clov-5-en-3-one (28).

The ketone was recovered unchanged after treatment with hydrogen at atmospheric pressure and room temperature under these conditions.

(i) Palladium-charcoal (10%) in ethyl acetate.
(ii) Palladium-charcoal (10%) in ethanol.
(iii) Platinum oxide in acetic acid.
(iv) Platinum oxide in acetic acid, containing perchloric acid.

Hydrogenation of the ketone (24, R=H).

When the ketone was shaken for twenty hours with palladium-charcoal (10%) in ethyl acetate, the hydrogen absorbed was equivalent to one half of the theoretical uptake. This was confirmed by the infra-red spectrum of the product, $\nu_{max.}$ = 1740-1690, 1630 $cm.^{-1}$ and by analysis with thin layer chromatography, which showed that the product consisted of a mixture of starting material (24, R=H) and the corresponding saturated ketone.

4-Desmethylclovan-3-one (81).

Complete reduction of the ketone (24, R=CH_3) to the corresponding saturated alcohol was accomplished by addition of a solution of the ketone (0.910g.) in ether (20 ml.) to a well stirred solution of lithium (0.4g.) in liquid ammonia (80 ml.). After two hours the excess lithium was carefully destroyed with wet ether, and dilute

brine added. Extraction with light petroleum afforded the expected alcohol, $\nu_{max.}$ = 3300 cm^{-1}, which was dissolved in acetone and treated at 0° with a solution (8N) of chromium trioxide in dilute sulphuric acid. After five minutes the mixture was diluted with brine and extracted thoroughly with light petroleum. The crude product (0.913g.) was adsorbed on alumina (Woelm, grade I, 30g.) and chromatographed; elution with light petroleum and ether-light petroleum (1:19) afforded the desired ketone (81) as a sweet-smelling, low-melting solid (0.630g.), $\nu_{max.}$ = 1740 cm^{-1}, which on recrystallisation from pentane afforded small white needles, m.p. 38-43° (Found: C, 81.85; H,10.70. $C_{14}H_{22}O$ requires C, 81.50; H, 10.75). The corresponding 2,4-dinitrophenylhydrazone recrystallised from ethanol-ethyl acetate as fine orange needles m.p. 165-171°, 176-178° (Found: C,62.20; H, 7.25; N,14.20. $C_{20}H_{26}N_4O_4$ requires C,62.15; H,6.80; N,14.30.).

The homogeneity of the ketone (81) was established by gas-liquid chromatography; on both 0.5% and 10% APL columns the ketone was eluted as a single component after 7.5 and 20.5 minutes, at 125° and 150° respectively, In addition it was observed that the ketone was developed as a single characteristic wine-coloured spot on thin layer chromatography.

(±)- Clovenic Anhydride (85).

(i) The ketone, 81, (0.650g.) was treated with a solution of furfural (2 ml.) in methanol (13 ml.) and aqueous potassium hydroxide solution (30%, 5 ml.) for eighteen hours at room temperature. The resultant deep red reaction mixture was diluted with brine and extracted

thoroughly with light petroleum. The combined extracts were washed with brine, dried over magnesium sulphate, and concentrated in vacuo to give the expected furfurylidene derivative of the ketone (81) as an orange oil (0.850g.), $\nu_{max.}$ = 3100, 1730-1700, 1600, 1540, 880,740 $cm.^{-1}$, $\lambda_{max.}$ = 333-335 mμ (14,500), which could not be induced to crystallise.

(ii) The crude furfurylidene derivative (0.850g.) was heated under reflux in an inert atmosphere for sixteen hours with a standard solution of sodium t-amylate (three equivalents) in benzene. The cooled solution was treated with methyl iodide (4 ml.) and reflux maintained for a further five hours. The reaction mixture was diluted with ice-cold brine and extracted with light petroleum. The combined extracts were washed with brine, dried over magnesium sulphate, and concentrated in vacuo to give a dark oil (0.826g.) which on trituration with light petroleum provided the furfurylidene derivative (84) of clovan-3-one (89) as a pale yellow solid (0.210g.) m.p. 105-108°. The latter on recrystallisation yielded large pale yellow prisms, m.p. 108-110°, $\lambda_{max.}$ = 333-335 mμ (22,100). (Found: C,80.55; H, 8.90. $C_{20}H_{26}O_2$ requires C, 80.50; H, 8.80.).

(iii) Ozone was passed through a solution of the ketone, 84, (0.210g.) in ethyl acetate (10 ml.) at -70° till the latter had assumed a blue coloration. The solution was concentrated in vacuo at 20° and the viscous residue taken up in acetic acid (6 ml.) and treated with hydrogen peroxide (30%, 2 ml.) for two hours on the steam bath. After evaporation of the solvent, the residue was extracted with ether and the combined extracts washed with aqueous sodium bicarbonate solution,

brine, and dried over magnesium sulphate. Removal of solvent afforded a crystalline solid m.p. 60-70° which was adsorbed on silica and chromatographed. Elution with light petroleum-ethyl acetate (49:1) furnished a colourless product which on recrystallisation provided (±)-clovenic anhydride (85) as colourless prisms, m.p.76-78°. (Found: C, 72.00; H,8.75. $C_{15}H_{22}O_3$ requires C,71.95; H,8.85). The infra-red spectrum of this synthetic material (CCl_4 solution) was entirely superposable on that of (-) - clovenic anhydride, m.p. 50-51° $\nu_{max.}$ = 1805, 1760, 1385, 1365 cm^{-1} (CCl_4 soln.). In addition, the derived clovenic acids (86) obtained by hydrolysis with aqueous sodium hydroxide solution exhibited the same melting point (180-184°d.), undepressed on admixture.

Attempted methylation of 4-desmethylclovan-3-one (81).

The ketone, 81, (0.100g.) was heated under reflux in an inert atmosphere for sixteen hours with a standard solution of sodium t-amylate (one equivalent) in benzene. After addition of methyl iodide (1 ml.) reflux was maintained for a further five hours before the addition of brine, followed by extraction with light petroleum. The crude product (0.096g.) was adsorbed on alumina (Woelm, grade I, 2g.) from light petroleum and chromatographed; elution with the latter solvent gave a pale yellow oil (0.020g.) $\nu_{max.}$ = 1740 cm^{-1}. However, the infra-red absorption between 1400 and 800 cm^{-1} confirmed that the product was a mixture of compounds, as expected, and no reaction of this type was subsequently attempted.

4-Desmethyl-2-hydroxymethyleneclovan-3-one (87, R=H).

A solution of the ketone, 81, (0.371g.) and ethyl formate (0.650g.) in benzene (1.5 ml.) was added dropwise with stirring to a suspension of freshly-prepared sodium methoxide (0.3g., dried at 180°/0.01 m.m. for three hours) in benzene (3.5 ml.) held at 0° under nitrogen. Over sixteen hours the initial gelatinous mixture gave way to a clear orange solution. The reaction mixture was diluted with an ice-cold aqueous solution of potassium chloride (10%, 20 ml.) and light petroleum (10 ml.) and the base-soluble derivative (87, R=H) separated. The organic layer was extracted several times with small volumes (5 ml.) of aqueous potassium chloride solution and the combined aqueous extracts then acidified with dilute hydrochloric acid and extracted with light petroleum. The combined extracts furnished a good yield (0.387g.) of a pale yellow oil (87, R=H), $\nu_{max.}$ = 1675, 1610, 1210, 1030, 820 $cm.^{-1}$, free of any starting ketone (81).

2-(N-Methylanilinomethylene) clovan-3-one (88, R=CH_3).

The ketone, 87, R=H, (0.524g.) was treated with a solution of N-methylaniline (0.32g.) in benzene (3 ml.) for sixteen hours. The solution was then concentrated in vacuo to give the desired product (88, R=H) as a viscous orange oil (0.730g.) $\nu_{max.}$ = 1675, 1610, 1570, 960, 920, 750 $cm.^{-1}$, which could not be induced to yield crystalline material. The crude product was treated for sixteen hours under nitrogen with a solution of potassium t-butoxide (five equivalents) in t-butanol (5 ml.) and benzene (5 ml.), and methyl iodide (2 ml.) was then added. After a further five hours, the reaction mixture was

diluted with brine and extracted with light petroleum to obtain the desired ketone (88, R=CH_3) as a dark oil (0.728g.) which could not be induced to yield crystalline material.

Clovan-3-one (89).

In an attempt to accomplish hydrolysis of 2-(N-methylanilinomethylene) clovan-3-one in one step, the latter was heated under reflux with aqueous sodium hydroxide solution (30%) but the product isolated clearly contained a high proportion of starting material.

In a two-step procedure the ketone, 88, R=CH_3 (0.698g.) was heated under reflux with a solution of hydrochloric acid (6N, 5 ml.) in methanol (5 ml.) for 1.5 hours to form 2-hydroxymethyleneclovan-3-one (87,R=CH_3) which was readily isolated by thorough extraction with light petroleum. The product obtained was heated under reflux with a solution of potassium hydroxide (2g.) in aqueous methanol (1:1, 10 ml.) for three hours, and the desired clovan-3-one (89) extracted from the cooled reaction mixture with light petroleum. The crude material (0.200g.) was adsorbed on alumina (Woelm, grade I, 5g.) from light petroleum and chromatographed; elution with this solvent afforded a low yield (0.120g.) of a mixture of clovan-3-one (89) and the starting ketone (81).

The above five-stage procedure for methylation of 4-desmethylclovan-3-one (81) was repeated with two modifications:

(i) the ketone (87,R=H) was condensed with N-methylaniline in solution in methanol

(ii) alkylation of the ketone (88,R=H) was accomplished by means of sodamide-methyliodide by heating this product under reflux with

the base (five equivalents) in benzene for three hours before addition of the alkyl halide. This procedure gave a low yield (20%) of clovan-3-one (89), $\nu_{max.}$ = 1740, 1385, 1365 cm^{-1}, differing in infra-red absorption from the ketone (81). Analysis by gas-liquid chromatography showed that the latter ketone was present to an extent of 5% in the product.

In the large conversion of the ketone (81) to clovan-3-one, the former (2.4g.) provided a good yield (1.844g.) of the vital ketone (89) by the above procedure. Thus the ketone (88, R=H) was heated under reflux for four hours under nitrogen with a suspension of sodamide (five equivalents) in benzene (25 ml.). After addition of methyl iodide (5 ml.) to the cooled mixture a gentle reflux was maintained for a further sixteen hours. The excess base was carefully decomposed with ice-cold brine and the mixture extracted thoroughly with light petroleum to give a dark oil (88, R=CH_3) which was hydrolysed by the two-stage procedure previously employed. In the base hydrolysis of the ketone (87, R=CH_3), however, methanol was omitted and the desired clovan-3-one (89) isolated by prolonged steam distillation which provided three fractions (i) 0.994g. (ii) 0.244g. (iii) 0.604g. identical in infra-red spectra, $\nu_{max.}$ = 1740, 1385, 1365 cm^{-1}. Analysis by gas-liquid chromatography; however, showed that although fractions (ii) and (iii) were quite homogeneous, fraction (i) contained a small proportion of the ketone (81). This observation was confirmed by thin layer chromatography, while fractions (ii) and (iii) were developed as characteristic blue spots, fraction (i) was developed as a blue spot with a marked reddish corona. Fraction (iii) on distillation afforded

pure clovan-3-one (89) as a colourless oil, b.p. 80°/0.03 m.m. (Found: C, 81.90; H, 10.90. $C_{15}H_{24}O$ requires C, 81.75; H,11.00), which gave an orange 2,4-dinitrophenylhydrazone (small needles from ethanol-ethyl acetate) m.p. 166-168° (Found: C,63.00; H,7.05; N, 14.00. $C_{21}H_{28}N_4O_4$ requires C, 62.95; H, 7.25; N, 14.15.)

Clovan-3-ol (90, R=H).

Clovan-3-one, 89, (0.244g.) was heated under reflux for three hours with a suspension of lithium aluminium hydride (0.122g.) in ether (10 ml.). The excess reagent was destroyed by careful addition of ice-cold brine, followed by dilute hydrochloric acid, and the mixture extracted thoroughly with ether. The resultant alcohol was obtained as a viscous oil (0.250g.) which slowly solidified; recrystallisation from pentane furnished clovan-3-ol as a crystalline epimeric mixture, m.p. 70-85° (Found: C, 81.75; H,11.40; $C_{15}H_{26}O$ requires C,81.05, H,11.80).

Clovan-3-yl ethyl carbonate (91).

Ethyl chloroformate (2 ml.) was added dropwise to a solution of clovan-3-ol, 90, R=H, (0.995g.)in pyridine (3 ml.) held at -10° and the mixture then allowed to stand at 5° for sixteen hours. The reaction mixture was acidified with a mixture of brine and dilute hydrochloric acid and extracted with light petroleum. The combined extracts were washed with brine, dried over magnesium sulphate, and concentrated in vacuo to give a pale yellow oil which on distillation provided the carbonate (91) as a colourless mobile oil (1.318g.), b.p. 120°/0.5m.m.,

$\nu_{max.}$ = 1740, 1385, 1365, 785 cm^{-1}. (Found: C,72.85; H,9.85. $C_{18}H_{30}O_3$ requires C, 73.45; H, 10.25).

(±)-Clovene (1).

A solution of clovan-3-yl ethyl carbonate, 91, (0.930g.) in silicone fluid (MS 200/1000 C.S., 1.5 ml.) was heated for hours in a metal bath held at 300 ± 5° under a mercury seal. After an initial vigorous reaction, the solution assumed a pale yellow coloration under gentle reflux. The product was isolated by rapid distillation at 0.03m.m. into a trap cooled in liquid nitrogen. Distillation afforded clovene (0.428g.) as a colourless oil, b.p. 48-52°/0.1 m.m., $\nu_{max.}$ = 3000, 1480, 1385, 1365, 745, 760 cm^{-1}, free of starting material, but contaminated with traces of silicone fluid. A sample of clovene (1) of unimpeachable purity, necessary for comparison with authentic (-) -clovene, was obtained via the crystalline epimeric dibromides (92). A solution of bromine (0.37g.) in carbon tetrachloride (3.7 ml.) was added over four hours to a solution of crude clovene (0.428g.) in the same solvent (4.28 ml.) held at 0° till a persistent red coloration was evident. The solution was stirred for a further sixteen hours at 5°, and four hours at room temperature before addition of a mixture of brine and aqueous sodium bicarbonate solution (1:1, 20 ml.). The resultant mixture was extracted thoroughly with light petroleum and the combined extracts washed with brine and dried over magnesium sulphate. Concentration of the solution in vacuo gave the dibromides as a viscous red oil (0.775g.) which on trituration with ethanol afforded a white crystalline epimeric mixture (0.458g.) of the dibromides (92) m.p.61-75°.

The purity of the product was established by thin layer chromatography, in which the dibromides were developed as a single characteristic violet spot.

To obtain pure (±) -clovene, the mixture of dibromides (0.400g.) was heated under reflux for sixteen hours with a suspension of zinc dust (0.200g.) in ethanol (4 ml.). The solution was diluted with light petroleum, filtered, washed with brine, dried over magnesium, sulphate, and concentrated in vacuo to give a pale yellow oil (0.229g.), which on distillation furnished (±) -clovene (1) as a colourless liquid (0.208g.), b.p. 80°/0.15 m.m., n_{21}^{D} = 1.4911, $\nu_{max.}$ = 3000, 1385, 1365, 760, 745 $cm.^{-1}$ (Found: C, 88.00; H,11.75. $C_{15}H_{24}$ requires C, 88.15; H,11.85), identical in all respects (infra-red, N.M.R., mass spectra, and gas-liquid chromatography) to similarly regenerated (-) -clovene, n_{19}^{D} = 1.4920.

4-Methyl-4-p-tolylpentan-2-one (30, R=H, R^1=CH_3).

This ketone, prepared in good yield (60%) by the method of Barnes and Buckwalter,[41] was a colourless liquid b.p. 130-132°/19 m.m., n_{21}^D =1.5080.

3-p-Tolylisovaleric acid (30, R=H, R^1=OH).

A solution of the ketone, 30, R=H, R^1=CH_3, (25g.) in dioxan (60 ml.) was added dropwise, with stirring, over two hours to a solution of sodium hypobromite, prepared by addition of bromine (9 ml.) to an ice-cold solution of sodium hydroxide (25g.) in water (200 ml.), held at 0-5°. When the aqueous solution had become colourless, stirring was maintained for a further three hours at room temperature. After removal of bromoform and dioxan by steam distillation, the alkaline solution was washed once with ether, acidified with dilute sulphuric acid (6N), and extracted with ether. The combined extracts were washed with brine, dried over magnesium sulphate and concentrated in vacuo to give a solid product which on recrystallisation from light petroleum afforded the desired acid as white needles, m.p. 76-78°, $\nu_{max.}$ = 1700, 1510, 820, 730 cm^{-1}. (Found: C, 74.45; H, 8.60. $C_{12}H_{16}O_2$ requires C, 74.95, H, 8.40.).

Attempted nitration of the acid (30, R=H, R^1=OH).

A mixture of fuming nitric acid (0.5 ml.), concentrated nitric acid (0.5 ml.) and concentrated sulphuric acid (1.3 ml.) was added dropwise with stirring to a solution of the acid (1.92g.) in concentrated sulphuric acid (3.3 ml.) held at 0-5°. After one hour the dark reaction

mixture was poured cautiously on to ice-cold brine and extracted thoroughly with ether. The resultant product, however, consisted of a dark viscous oil which could not be induced to yield crystalline material.

3-Methoxy-4-methylacetophenone.

This ketone was obtained in four steps, as a colourless low melting solid, according to the method of Lindahl.[44]

1,1-Dicyano-2-(3-methoxy-4-methylphenyl) propene (31, R=CN).

3-Methoxy-4-methylacetophenone (6.015g.) was heated under reflux with a solution of malononitrile (2.475g.) in benzene (30 ml.) containing acetic acid (0.5 ml.) and ammonium acetate (1g.), in a Dean and Starke apparatus. When evolution of water had ceased, the solution was taken up in ether, washed with brine containing aqueous sodium bicarbonate solution, dried over magnesium sulphate, and concentrated in vacuo to give a yellow solid which on recrystallisation from light petroleum provided the dinitrile (31, R=CN) as fine white needles (2.3g.), m.p. 97-98°, $\nu_{max.}$ = 2250, 1610, 1570, 1240 cm^{-1}, $\lambda_{max.}$ = 240, 253, 315 mμ (Found: C, 73.50; H,5.25; N,13.00. $C_{13}H_{12}N_2O$ requires C,73.55; H,5.70; N,13.20.)

1,1-Dicyano-2-methyl-2-(3-methoxy-4-methylphenyl) propane (32,R=CN).

An ethereal solution of methylmagnesium iodide, prepared from magnesium (0.37g.), was added dropwise with stirring to a solution of the unsaturated dinitrile, 31, R=CN, (1.54g.) in ether (20 ml.). The opaque yellow mixture initially formed, rapidly afforded a clear orange

complex insoluble in the supernatant ether. After ten minutes, the complex was decomposed by means of aqueous ammonium chloride solution and thoroughly extracted with ether. The product consisted of a pale yellow solid, which on recrystallisation from light petroleum furnished the saturated dinitrile (32, R=CN) as white needles (1.25g.), m.p.73-74° $\nu_{max.}$ = 2300, 1030, 870, 820 $cm.^{-1}$ (Found: C,73.75; H,7.40; N,12.30. $C_{14}H_{16}N_2O$ requires C, 73.65; H, 7.05; N,12.25.).

β-(3-Methoxy-4-methylphenyl) isovaleric acid (30, R=CH_3O, R^1=OH).

The dinitrile, 32, R=CN, (1.15g.) was heated under reflux for three days with a solution of potassium hydroxide (3g.) in water (7 ml.). After acidification of the cooled solution, ether extraction yielded the expected acid (32,R=COOH) as a white solid (0.8g.) which on recrystallisation gave small colourless prisms m.p. 142-143°. (Found: C,63.25; H,6.75. $C_{14}H_{18}O_5$ requires C,63.15; H,6.80.).

This acid when heated at 160°/19 m.m. readily afforded the desired acid (30, R=CH_3O, R^1=OH) as a white solid (0.5g.) which on recrystallisation from light petroleum was obtained as small needles m.p. 64-65°, $\nu_{max.}$ = 3500-2700, 1250 $cm.^{-1}$ (Found: C, 70.25; H, 7.90. $C_{13}H_{18}O_3$ requires C,70.25; H,8.15.).

Ethyl α-cyano-β-(3-methoxy-4-methylphenyl) acrylate (31,R=$COOC_2H_5$).

3-Methoxy-4-methylacetophenone (4.1g.) was condensed with ethyl cyanoacetate (2.83g.) in the manner previously described for the malononitrile condensation. The desired product (2.4g.) which crystallised from the reaction mixture, on recrystallisation from

light petroleum afforded the ester (31, R=$COOC_2H_5$) as white needles m.p. 97-98°, $\nu_{max.}$ = 1720, 1680, 1610, 1590, 1250 cm^{-1}. (Found: C,69.25; H,6.55; N, 5.40. $C_{15}H_{17}NO_3$ requires C,69.50; H,6.60; N,5.40.).

When this cyano-ester was treated with Grignard reagent as in the case of the dinitrile (31, R=CN) only starting material was recovered unchanged, despite the use of freshly-prepared cuprous chloride.[104]

Ethyl α-formylisobutyrate (94) and its diethyl acetal.

The acetal was obtained as a colourless, sweet-smelling, liquid b.p. 104-107°/19 m.m., n_{19}^{D} 1.4168, according to Deno.[96] Acid hydrolysis readily afforded the corresponding aldehyde (94) as a colourless liquid, b.p. 62-64°/19 m.m., n_{21}^{D} = 1.4110.

γ-Carbethoxy-γ,γ-dimethylcrotonaldehyde (95)

A solution of ethyl vinyl ether (1g.) in benzene (5 ml.) was added dropwise, with stirring, to a solution of the acetal, of 94 (3g.) in benzene (12 ml.) containing boron trifluoride etherate (0.1 ml.) held at 30-35°. The solution was then stirred at 45° till the pale yellow colour had given way to an intense purple. The reaction mixture was then taken up in ether, washed with a mixture of brine and aqueous sodium acetate solution, dried over magnesium sulphate, and concentrated in vacuo to give a pale yellow oil (3g.) identical in infra-red absorption with the starting material (95), $\nu_{max.}$ = 1720, 1385, 1365, 1200-1000 cm^{-1}.

A solution of ethyl vinyl ether (3.54 ml.) in benzene (10 ml.) was added dropwise, with stirring, to a solution of the aldehyde, 94 (8.65g.) in benzene (12 ml.) containing boron trifluoride etherate

(0.1 ml.) held at 30-35°. The solution was then heated for one hour at 35°, and a further hour at 45°. Isolation of the product as before yielded a red oil (11.3g.) which was heated under reflux with a solution of acetic acid (60 ml.) in water (40 ml.) containing hydrochloric acid (6N, 0.1 ml.) for three hours. The cooled mixture was diluted with water (400 ml.) and extracted with light petroleum, the combined extracts were washed with aqueous sodium bicarbonate solution, brine, dried over magnesium sulphate, and concentrated in vacuo to give a dark orange oil (8g.) which on fractional distillation furnished a large proportion of starting aldehyde (94), and also the desired aldehyde, 95, (1.5g.) as a pale yellow oil, b.p. 98-108°/19 m.m. Redistillation afforded a pale yellow liquid, b.p. 108-110°/19m.m., $\nu_{max.}$ = 2700, 1725, 1690, 1630 cm^{-1}., $\lambda_{max.}$ = 218-220 mμ(13,400).

Attempted Michael reaction.

A solution of 2-carbethoxy-6-methylcyclohexanone (0.440g.) and the aldehyde, 95, (0.406g.) in ethanol (2 ml.) was added dropwise with stirring to a solution of sodium (0.002g.) in the same solvent (5 ml.) held at -15°. Since the intensity of the ultra-violet absorption underwent no appreciable change after seventeen hours at room temperature, the solution was heated under reflux. The reaction mixture darkened rapidly, however, and the product isolated consisted of a deep red viscous oil which afforded no homogeneous fractions on distillation.

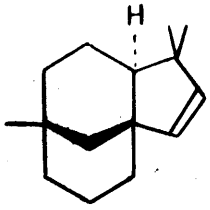
Attempted carboxylation of carvone (102).

A mixture of carvone (5g.) and formic acid (2.3g.) was added in pentane (5 ml.) with stirring to concentrated sulphuric acid (12 ml.)

held at 0^{o} over two hours. The mixture was allowed to stand at room temperature for a further two hours, and then poured on to ice-cold brine and extracted with light petroleum. The dark yellow oil thus obtained was found to be identical to carvone, and no trace of the desired acid (100, R=H) was observed.

Acyloin condensation of dimethyl clovenate.

A solution of dimethylclovenate, prepared by the addition of diazomethane to clovenic acid, 86, (0.750g.), in ether (50 ml.), was added to a solution of sodium (seven equivalents) in redistilled, anhydrous, liquid ammonia, over one hour under nitrogen. After four hours, the last traces of ammonia were removed in a vigorous current of nitrogen and excess sodium destroyed by means of a solution of methanol in ether (2%, 50 ml.). Extraction afforded a neutral pink oil (0.100g.), $\nu_{max.}$ = 3400, 1740 cm^{-1}, and a large fraction soluble in aqueous sodium carbonate solution. Before aerial of the pink keto-clovanol could take place, the latter was reduced to a viscous diol (90,R=OH) which did not yield any crystalline material.



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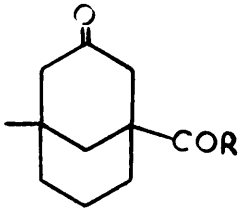

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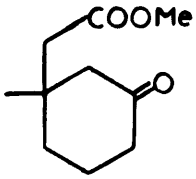

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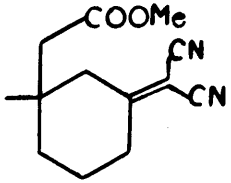

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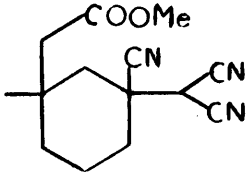

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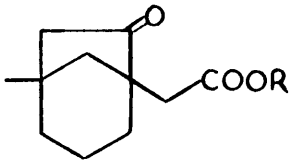

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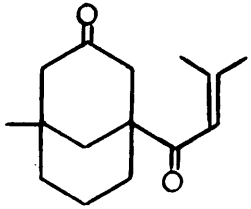

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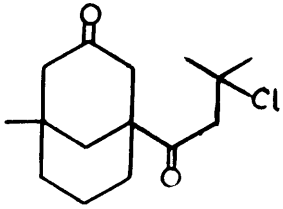

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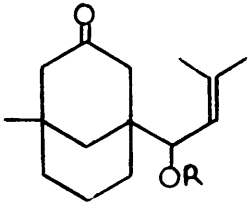

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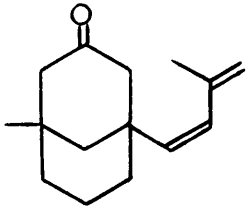

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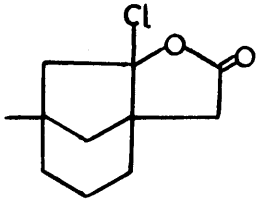

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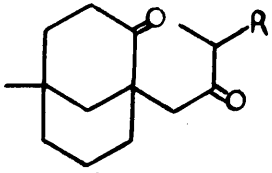

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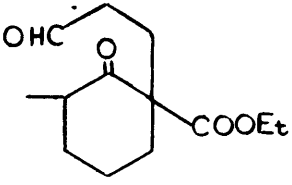

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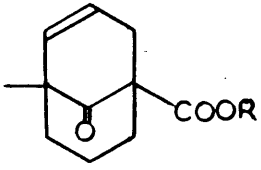

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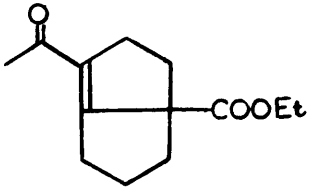

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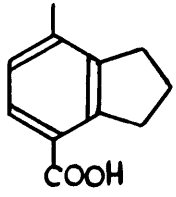

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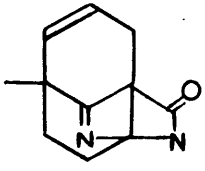

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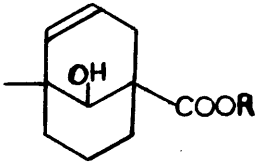

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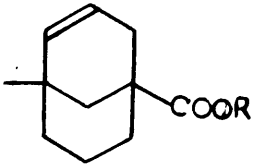

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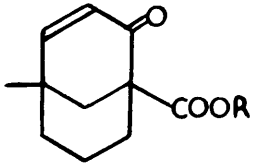

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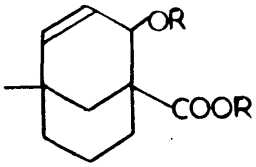

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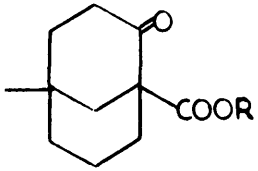

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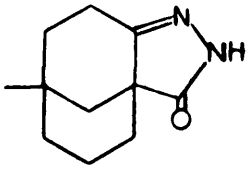

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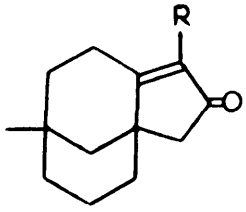

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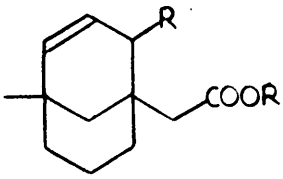

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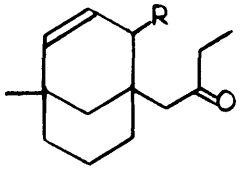

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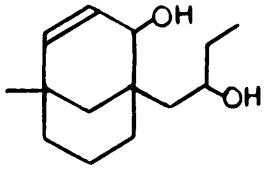

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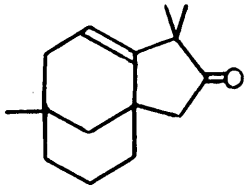

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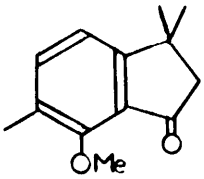

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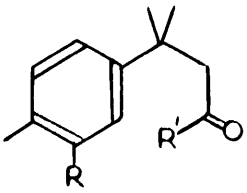

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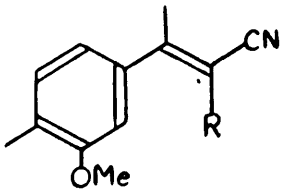

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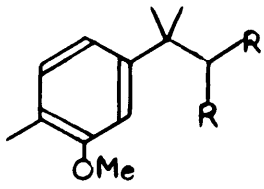

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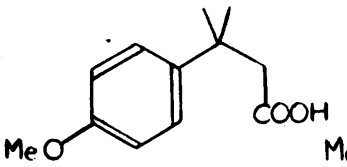

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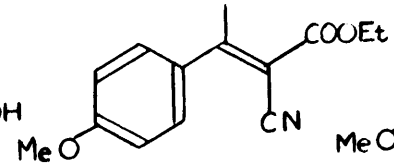

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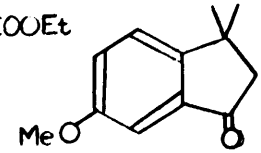

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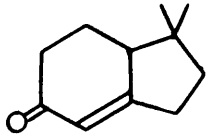

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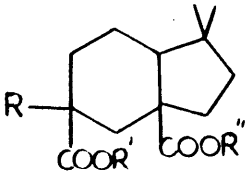

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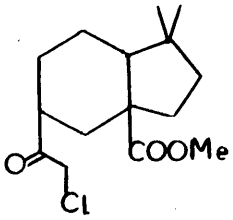

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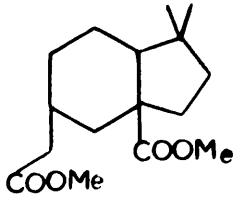

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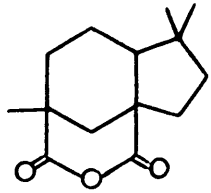

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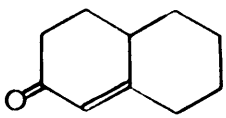

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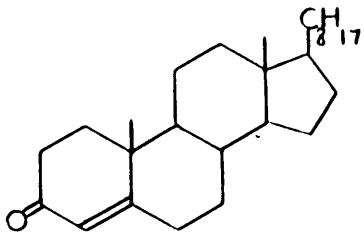

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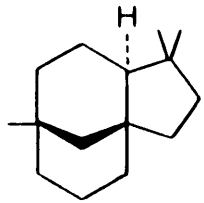

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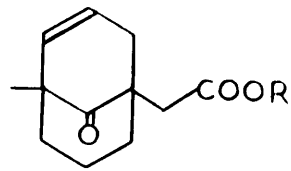

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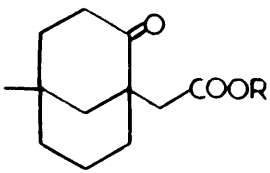

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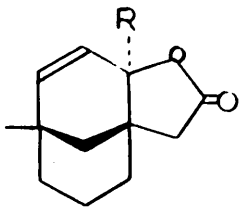

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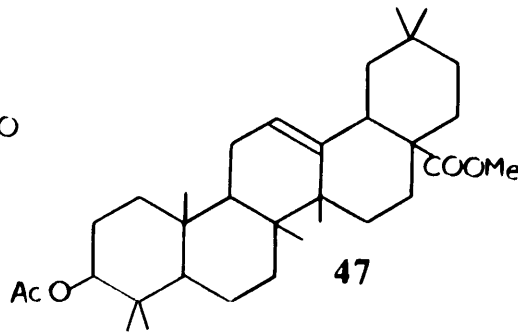

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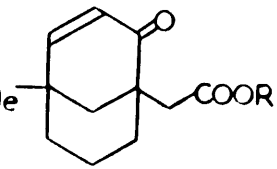

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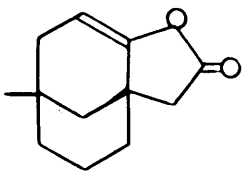

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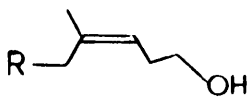

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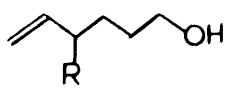

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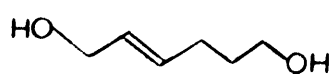

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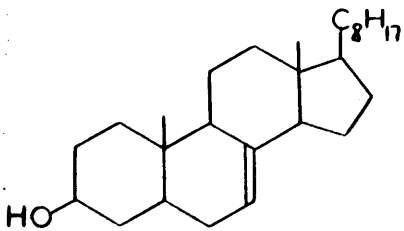

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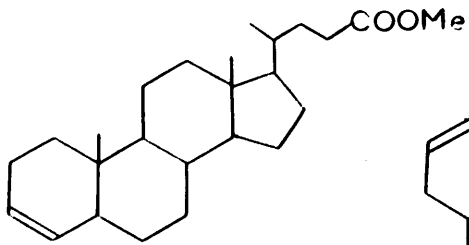

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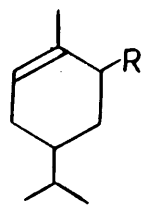

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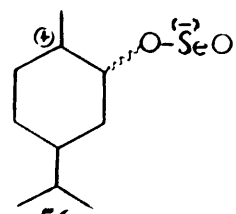

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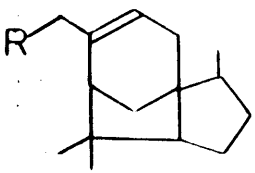

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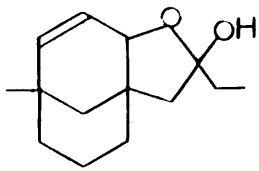

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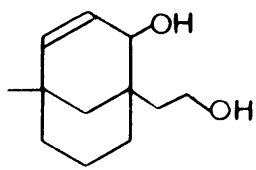

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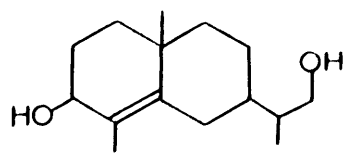

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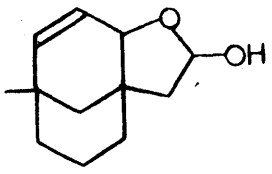

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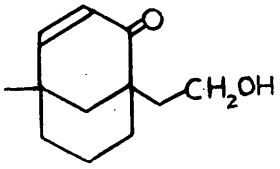

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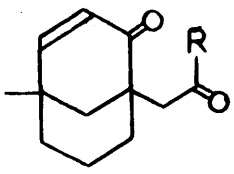

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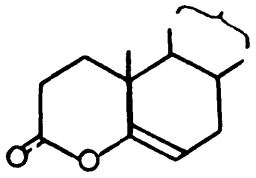

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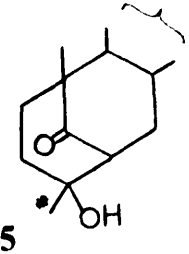

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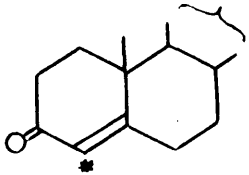

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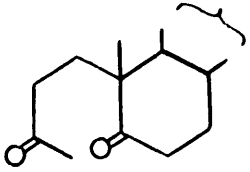

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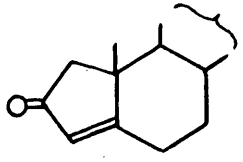

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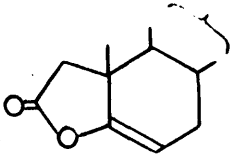

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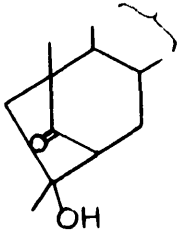

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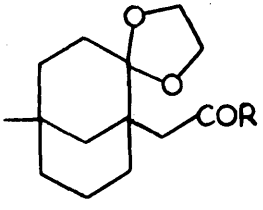

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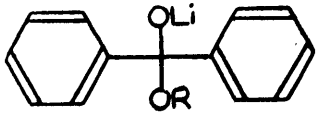

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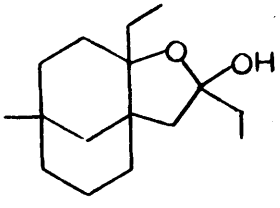

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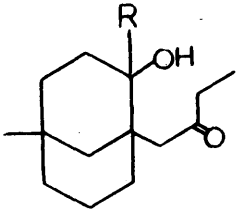

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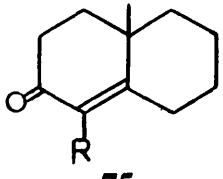

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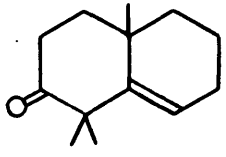

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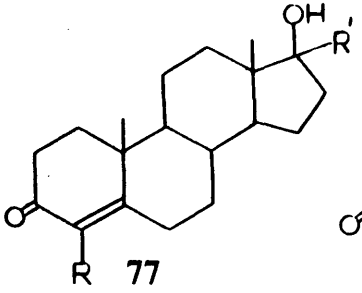

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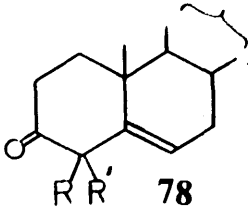

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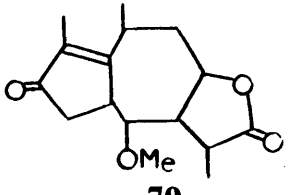

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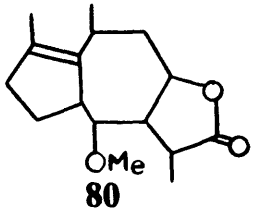

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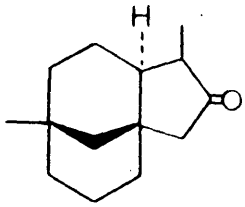

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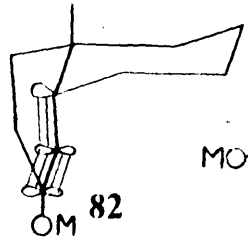

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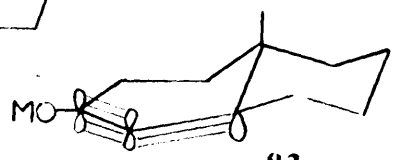

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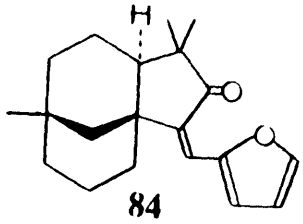

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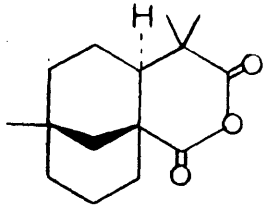

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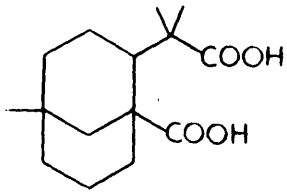

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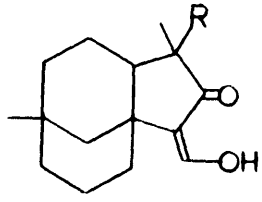

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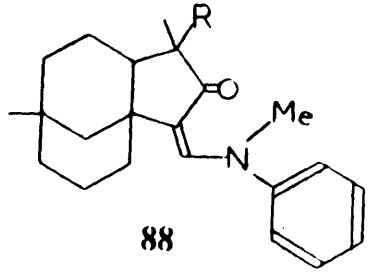

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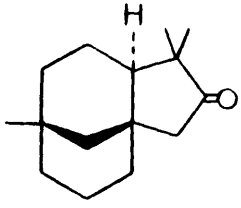

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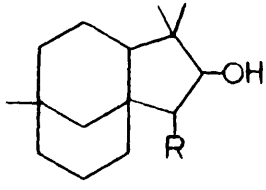

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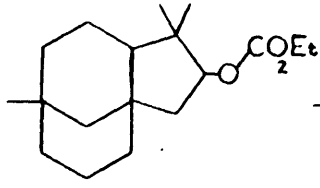

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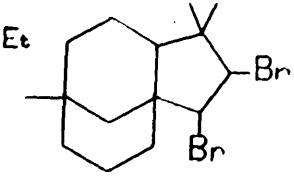

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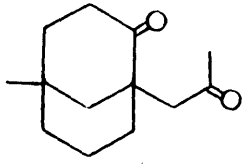

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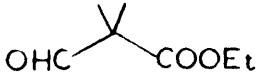

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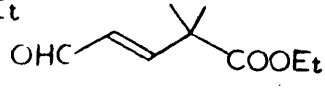

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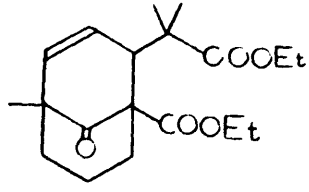

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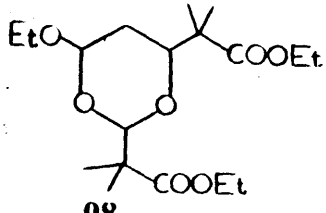

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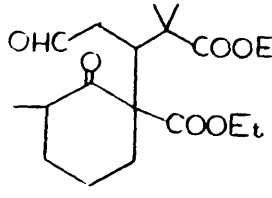

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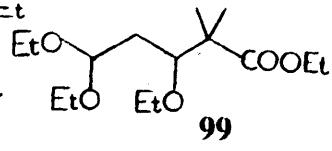

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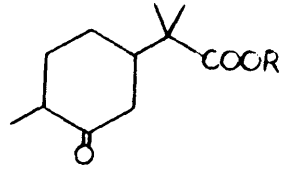

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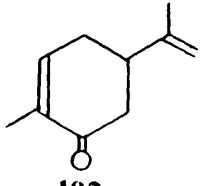

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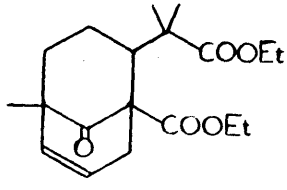

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